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# International Medical and Surgical Survey

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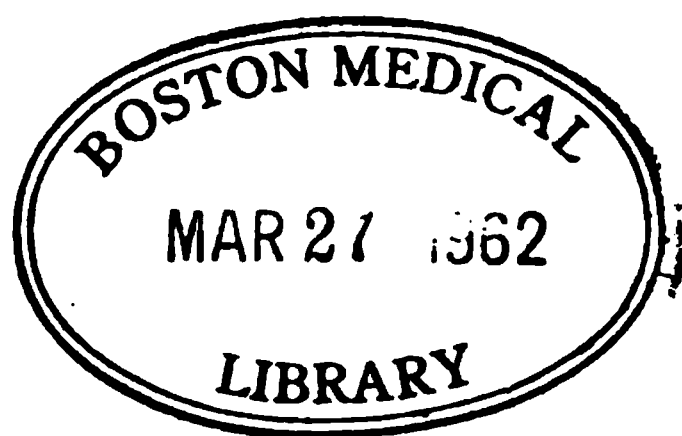
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**SECTION 1—ANATOMY, PHYSIOLOGY AND  
BACTERIOLOGY.**

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**SECTION 1. ANATOMY, PHYSIOLOGY AND  
BACTERIOLOGY.**

**1a. ANATOMY AND PHYSIOLOGY.**

(1a—1)

(1a—1)

**Albumin or Endosperm?**

*Biagio Longo, Riv. di biol., 4: 170, Rome, March-April, 1922.*

In the gymnosperms, following division of the nucleus of the embryonic sac, there is formed in the interior of the sac a tissue rich in reserve substance, composed of a certain number of cells—the endosperm. At the extremity of the endosperm we differentiate the archigoniums, whose oval cells, fertilized, give origin to the embryos, which, during the germination of the seed, consume all the material of the endosperm.

In angiosperms, on the contrary, the alimentary tissue of reserve for the embryo is differentiated after fertilization, and in 2 different ways: usually it forms in the interior of the embryonal sac, sometimes outside. While in the gymnosperm the tissue of reserve is a true protalla, in the angiosperm, when it originates in the interior of the embryonal sac, it should be considered as the brother of the embryo (and this, notwithstanding it must be digested by the embryo itself); when, on the other hand, it originates outside of the sac, it has the value of a megasporangium.

Considering also the double fertilization that there is in the angiosperm and not in the gymnosperm, it is not possible to designate with the same name of endosperm the nutritious tissue that forms within the embryonal sac of the gymnosperm and that which forms within the embryonal sac of the angiosperm, these being of different morphological values.

The writer is an adherent of the nomenclature proposed by Schleiden and Vogel, who gave the name of endosperm to the nutritional tissue that forms in the interior and perisperm to that which forms external to the embryonal sac, designated by preceding authors as albumin. He thus obviates the confusion likely to arise from the use of the name endosperm indiscriminately for the gymnosperm and the angiosperm, even if these are denominated respectively "primary" and "secondary" endosperm.

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(1a—2)

(1a—2)

**The Estrous Cycle in the Mouse.**

*Edgar Allen, Am. J. Anat., 30: 297, May 15, 1922.*

In the author's studies more than 90 animals were used, the majority being young virgin mice, although a few that had borne litters were included for comparison. The stock chosen included brown, black, albino, dominant white with black eyes, gray, agouti, and yellow, as well as hybrids of these strains. The animals were well fed and kept in healthful environmental conditions. As a criterion of the condition of heat the cell content of the vaginal fluid was used. The condition



of the vulva, the degree of opening of the vagina, and the nature of the vaginal contents were noted daily. A histological examination of the smears was always the deciding factor in the diagnosis, the smears being made by the usual bacteriological technic and hematoxylin and aqueous eosin used as stains. In a series of 27 animals, observations were made daily for about five weeks before killing in order to obtain an accurate record of the number and duration of estrous periods as an aid to the interpretation of ovarian conditions. Then the animals were killed and the histological examination of the internal and external genital organs was made. The author found that the external signs are unreliable criteria of estrus in mice, the presence of cornified cells in the vaginal smear being a more accurate indication. When these cells appear in masses, ovulation has usually occurred. The chief changes in the vaginal epithelium are its rapid growth, the formation of a stratum corneum, and (after ovulation) its degeneration and removal by leucocytosis. The stratum germinativum is also partly destroyed. It may grow from four to six or twelve or thirteen layers in thickness in one day. There is considerable degeneration and leucocytosis in the uterine epithelium which is, however, seldom removed from the stroma. Bleeding rarely occurs in the mouse, but a heavy leucocytic infiltration takes place during the metestrus (*metestrus* refers to the period of return to the diestrous condition, which latter is the period of relative quiescence). Periodic degenerative changes in the oviduct parallel those in the rest of the genital tract, and are evidenced in extrusion of nuclei from the ciliated epithelium. The author observed that in mice that ovulate spontaneously 2 or 3 sets of corpora lutea of estrus may be present at all times; in mice that do not ovulate spontaneously corpora lutea may be entirely absent, and yet normal estrous cycles are experienced in both types of animals. Allen therefore concludes that they have no primary causative relation to estrous changes in the genital tract.

(1a—3)

(1a—3)

#### **The Action of Ultraviolet Rays on Starfish Eggs.**

*Ralph S. Lillie and Margaret L. Baskervill, Am. J. Physiol., 61: 57, June 1, 1922.*

Most of the authors' experiments were performed on unfertilized eggs. The source of ultraviolet light was a small mercury arc quartz lamp (arc about 8 cm. long), running on a potential of 100 to 110 volts with a direct current of 1.5-2 amperes. The lamp was enclosed in a rectangular wooden box painted black inside and out and ventilated. The eggs were exposed in a layer of sea-water 1 cm. deep in a flat-bottomed uncovered glass dish, placed inside the box vertically below the horizontal arc; they were allowed to settle before exposure to the rays, and never formed more than a single layer thick. The temperature inside the box was kept between 18 and 20°. The distance of the bottom of the dish from the arc was about 15 cm., and the quantity of radiation received by the eggs was varied by varying time of exposure. The authors' studies with unfertilized eggs included (1) direct structural changes produced by ultraviolet radiation; (2) activation by ultraviolet radiation alone; (3) effects of radiation applied before breakdown of germinal vesicle; (4) effects of radiation on the response of sperm

fertilization; (5) influence of brief radiation on activation by high temperature; (6) radiation followed by treatment with warm sea-water; (7) warm sea-water treatment followed by radiation; (8) influence of brief radiation on activation by butyric acid. The action of radiation on motility and fertilizing power of spermatozoa was also studied. The authors found that brief exposure (2-7 minutes) of unfertilized starfish eggs to the rays described causes imperfect separation of fertilization-membranes followed by slow cleavage. The activation produced is only partial, although occasionally a blastula is formed. Complete activation is never obtained with radiation alone, apparently because of the injurious secondary action of the rays. Longer radiation causes local cytolytic effects which may spread and involve the whole egg. Normal eggs exposed to ultraviolet radiation for varying times and then fertilized with normal sperm exhibit abnormalities of the following kind, which increase with length of radiation: interference with separation of fertilization-membranes; retarded and asymmetric cleavage; irregular development and early cessation of development. The susceptibility to injury and also to activation by rays is greatest in the postmaturation period. In the case of eggs which give an imperfect or partial response to sperm-fertilization, a brief radiation applied shortly before fertilization often has a favorable influence upon the subsequent development. Brief preliminary radiation of unfertilized eggs shortens the time required to produce activation by fatty acid and high temperature. Radiation following partial activation by fatty acid or heat is ineffective in promoting activation. The authors found that ultraviolet rays rapidly decrease the motility and destroy the fertilizing power of spermatozoa.

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(1a—4)

#### **A Ten Year Old Strain of Fibroblasts.**

*Albert H. Ebeling, J. Exper. Med., 35:755, June 1, 1922.*

At the Rockefeller Institute, there has been under cultivation for 10 years a strain of fibroblasts obtained originally from the heart of a chick embryo, the present cultures representing the eighteen hundred and sixtieth generation of the connective tissue cells. There has been no change during this period in the appearance of the cultures, and growth is as rapid now as at any time, each fragment, as a rule, doubling in size in 48 hours. In the 10 years more than 30,000 cultures have been derived from the original piece of heart muscle less than 1 c. mm. in size, and it is estimated that if all the tissues had been allowed to multiply to their greatest extent the mass would now be very much larger than the sun. It is thus evident that the cells are able to transform the foodstuff of the medium into protoplasm, and also that the cells are potentially immortal.

The existence of this pure strain of cells has made it possible to study certain biologic and physiologic problems. It has been used for the detection of substances in the humors which increase or decrease the rate of cell proliferation, demonstrating the presence in embryonic juice of a factor increasing cell multiplication to a high degree, and the fact that adult serum, on the contrary, has an inhibiting effect on growth, which increases with the age of the animal from which it is obtained. It has been shown, further, that the cells remain young or

grow old, depending, not on the amount of potential energy they contain, but on the food material they are given and the extent of elimination of their catabolic substances. The strain has also been useful in the study of some of the processes of immunity.

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(1a—5)

(1a—5)

**The Influence of the Forces of Occlusion on the Development of the Bones of the Skull.**

*Lawrence W. Baker, Internat. J. Orthodont., Oral Surg. & Radiog., 8: 259, May, 1922.*

The muscles of mastication to a large extent surround the cranium, extending from the temporal ridge on one side to the temporal ridge on the other side, and the internal muscles of mastication are attached surprisingly close to the base of the brain. These muscles are attached to the skull and inserted into the mandible at many different places and in many different ways, so that they pull in as many different directions. But it is a singular fact that, varied as are these muscles in shape, size, power and action, they have one common function, the dental equipment. The teeth may almost be termed the fulcrum of this group of muscles, because it is only when the teeth are brought together forcibly, or come in contact with food in mastication, that the great power of these muscles is brought out. It occurred to the writer that if his hypothesis regarding the influence of the dental equipment on the formation of the bones of the head were correct, interference with the laws of occlusion in the lower animals should show consequent effects in the formation of the bones of the skull; and if variation occurred, it might throw some light on the most complex problem of the development of the human head. To test this theory, the following experiment was performed: A litter of 4 rabbits was selected at the age of weaning. One of the rabbits was chloroformed, and the skull procured. Two of the remaining animals were operated on by grinding down all the teeth on the right side of the mandible and the maxillary right central incisor. As the teeth elongated, repeated grinding rendered them useless, so that all the mastication was performed on the left side. The fourth rabbit was kept in a normal state for comparison. After 7 months, the skull of one of the rabbits showed on the upper aspect a deviation of the bones to the left. The suture between the parietal and frontal bones did not run strictly at right angles to the longitudinal axis of the skull; the right frontal bone projected farther forward than the left; also, the left zygomatic space was longer and more advanced than the right. The most noticeable deviation was in the nasal bones, both being twisted to the left. On the lower aspect, the deviation extended throughout the entire skull, the most remarkable being that of the anterior root of the right zygomatic arch (the zygomatic process of the maxillary bone) which was retreated, while the body of the right maxillary bone itself, with the teeth that it contained, was greatly advanced. The mandible was also distorted, even to the size of the articular processes of the condyles. The one on the left, on the working side, was perceptibly larger than the one on the right. Three weeks later autopsies were performed upon the second altered rabbit, and on the normal animal. In dissecting out the muscles that control the move-

ments of the mandible, the writer was struck with the unequal muscular development of each lateral half of the altered animal. Both experimental skulls weighed much less than the normal skull, showing that evidently the interference had affected the general osseous development of the head.

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(1a—6)

**The Mechanics of the Temporomandibular Articulation.**

*Fritz Worthmann, Anat. Anz., 55: 305, Jena, April 30, 1922.*

Worthmann endeavored to determine whether the dense, ivory-like texture of the petrosa is ascribable merely to its function as the reinforcing rib of the cranial vault or also to its participation in the function of the temporomandibular articulation. For this purpose he studied the cranium in predatory animals as these are destitute of the external pterygoid muscle, and the temporomandibular articulation has the movement of a simple hinge joint. The muscles of mastication are divisible into 2 groups according to the direction of their pull: (1) an anterior one, consisting of the internal pterygoid and masseter, which transmits the pressure only to the facial skeleton, and (2) a posterior group, represented by the temporal muscle, which transmits it also to the cranium. The action of each muscle may be represented by a single straight line connecting the centers of the surfaces of origin and insertion. In the case of the first 2 muscles, this axis falls vertically on the center of the line connecting the temporomandibular articulation with the contact surface of the last pair of molars; in the case of the temporal muscle, it falls obliquely on the prolongation of this line within the dental arches. Resolved into its components, the one acting in the direction of the temporomandibular articulation is greater than that of mastication pressure. Articular pressure is offset by reinforcements in the skull to which the petrosa belongs. As the temporal muscle is the only muscle transmitting maxillary power to the cranium and thence to the cervical musculature, it is developed most strongly in those animals who are compelled to carry great weights between the maxillas. In man the action of the internal pterygoid serves to compensate for the underdevelopment of the coronoid process and its unfavorable influence on the utilization of the temporal muscle's power with opened mouth, to keep the articular component of the temporal muscle's pressure from the cranium, and to render possible the isolated action of the incisors in biting.

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(1a—7)

(1a—7)

**The Origin of the Cerebral Cortex. A Phylogenetic and Neurobiotactic Study.**

*H. Kuhlenbeck, Anat. Anz., 55: 338, Jena, May 20, 1922.*

The phylogenesis of the cerebral cortex can be considered from a morphogenetic or histogenetic point of view. Under morphogenesis the author considers extent, form and distribution of the cerebral cortex as well as the homologues of the segments of the cortex with the primordial fields of the precortex. The histogenesis of the cerebrum comprises the formation of specific cellular elements and the tendency to characteristic processes of stratification. The brain of urodeles serves best

as the starting point in such a study. The primordial elements of the cerebrum of vertebrates is represented by the pallium, base and formatio lobaris; the cerebral cortex originates from the pallium as well as from the base. Before the development of the cortex there are already primordial fields of the later cortex. While the neopallium in urodeles appears first in the area lateralis of the pallium, there is a dorsomedial archipallial primordium very early in phylogenesis (petromyzon, selachians). As a transition between urodeles and amphibia there is in the gymnophions a posterior area ventrolateralis; in the reptiles the primordial fields are already developed into true cortical fields, the area medialis and area dorsalis as an archicortex, the area lateralis as a neocortex, and the area ventrolateralis anterior and posterior as a paleocortex. The reptile stage is a nodal point in the line of brain development between the bird type on the one hand and the mammalian type on the other hand, the latter being characterized by a powerful development of the cortical structure. The archicortex of reptiles corresponds to the cortex heterogeneticus rudimentarius of mammals, the neopallium to the cortex heterogeneticus striatus of mammals. The designations homogenetic and heterogenetic are based on cyto-architectonic and partly ontogenetic observations, those formations being regarded as homogenetic in which the cellular tectonics show a 6-layered fundamental type, while the heterogenetic cortex, even in the early stages of fetal life, deviates from the 6-layered fundamental type. To the cortex heterogeneticus belong the cornu ammonis, the fascia dentata, the subiculum, the indusium griseum and the septum pellucidum. The histogenetic formation of the cortex follows the laws of neurobiotaxis both in phylogenesis and ontogenesis. In the process of stratification the cortex of the mammals does not follow that of the reptiles. In the heterogenetic cortex there is a stratification into 3 layers, corresponding to the archicortex of the reptiles, a zonal layer and an internal and external cellular layer, but the homogenetic cortex of mammals shows a fundamental structure of 6 layers, which does not exist in the neocortex of reptiles.

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(1a—8)

(1a—8)

**The Intercolumnar Tubercle, an Undescribed Area in the Anterior Wall of the Third Ventricle.**

*Tracy Jackson Putnam, Bull. Johns Hopkins Hosp., 33: 181, May, 1922.*

A structure is here described for the first time, lying in the anterior wall of the third ventricle of the mammalian brain. It appears to be analogous in many ways to the well-known areae postremae of the fourth ventricle. It is a small prominence about 1 mm. in diameter, situated between the columns of the fornix, at the level of the upper border of the foramen of Monro, below the juncture of the two lateral choroid plexuses. Putnam suggests the name "intercolumnar tubercle" for this structure. Histologically it is composed of a peculiar loose neuroglial tissue containing many coarse capillaries, and covered by a low ependyma. In the human brain it contains a few small nerve cells; the monkey (*Macacus rhesus*) also contains in this area cells somewhat resembling nerve-cells, but they are not found in lower mammals. In this tubercle, as in the areae postremae, but nowhere else in the brain.



the adventitia of the capillaries takes up trypan blue and similar dyes during life. No function can as yet be assigned for the intercolumnar tubercle.

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(1a—9)

(1a—9)

**A Rudimentary Epithelial Organ in the Prefrenular Floor of the Mouth in Mammals.**

*Ernst Keller, Anat. Anz., 55:265, Jena, April 15, 1922.*

This organ, which was described macroscopically by Ackerknecht in domestic animals, has been examined histologically by Keller. Macroscopically the mucous membrane of the mouth shows paired and symmetric depressions back of the first incisor near the median plane. These depressions may be punctate, or they may be fine grooves. In the primates between the first incisors 2 longish or punctate, generally asymmetric, depressions are visible, but in man this structure is not seen. Microscopically, Ackerknecht's organ seems to be a sacculated or solid epithelial shoot, which varies greatly in form and number in different individuals. As a rule it runs as an independent anlage in the propria obliquely downward and backward, then bends toward the tongue and terminates in a free end. In hogs, dogs and rabbits it lies horizontally just beneath the papillary bodies of the neighboring mucous membrane and merges in the posterior segments of it with the epithelium of the surface to form a sort of roll. In all animals except cats there are solid as well as hollow forms of the epithelial bud. The lumen of the hollow organ is generally lined with horny tissue, more rarely with clear, indifferent cells. The opening often continues toward the teeth in a furrow. This form generally occurs in equine animals and ruminants. The organ is in general poor in pigment but in dogs there is a dense axial strip of pigment. The organ is a pure invagination of the epithelium and is, like the papillas, formed in the direction of the greatest pressure. The marked individual variations show the rudimentary character of the organ, which as a matter of fact has lost its function in mammals. In reptiles there is an anterior sublingual gland consisting of an anterior and 2 posterior branches which diverge toward the tongue. The position of the anterior one corresponds to that of this rudimentary organ. The formation of functioning gland cells is prevented in mammals by changed mechanical conditions, but the anlage persists.

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(1a—10)

(1a—10)

**Anatomic Notes on the Precordial Wall of the Thorax.**

*Cosimo Rubino, Anat. Anz., 55:412, Jena, April 15, 1922.*

The apex beat which lifts the intercostal spaces cannot be without effect on the symmetry of the thoracic wall. It is found that, as a matter of fact, the fifth left intercostal space is almost always wider than the right, but that in cases of dextrocardia the right fifth space is the widest. The mediastinal surface of the sternum has at the point of insertion of the fourth to the sixth costal cartilages an excavation which has a pronounced tendency toward the left sternal border. The fourth, fifth and sixth costal cartilages run more obliquely on the left than on the right, and on the inner surface there is a depression which is at

the fourth in new-born infants and at the fifth costal cartilage in adults. The fibers of the intercostal muscles are more numerous and thicker on the left side than the right and run somewhat more steeply.

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(1a—11)

**The Lungs of Polypterids.**

*M. Rauther, Anat. Anz., 55:290, Jena, April 15, 1922.*

The air-sacs of *Calamoichthys calabaricus*, which is closely related to polypterus, are very similar in form and arrangement to those of the latter. Their walls, aside from the peritoneal covering, consist of: (1) 2 layers of muscle; (2) a loose connective tissue layer, and (3) the epithelium. On the surface, longitudinal folds are noted in which small blood vessels run; these connect the great transverse branches of the arteries and veins of the air-sacs. These fine branches, however, are not the last divisions of the vessels; there is in addition a dense capillary network with the closest connection with the epithelial surface. The air-sacs are characterized by this as respiratory organs. The vascularized longitudinal folds of the lungs of polypterids are probably the equivalents of the alveoli of true lungs.

While in polypterus the glottis leads into a short, nonpaired cavity, the condition is not the same in the calamoichthys, as in the latter the furrow passing from the larynx is in direct, open connection only with the right lung. The left lung communicates only indirectly with the esophagus, while in the posterior part of the glottis the fused median walls of the 2 air-sacs are penetrated by an oval opening. Therefore, in the polypterid lung the left pair has become merely an appendage to the dominating right one.

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(1a—12)

**The Terminals of the Human Bronchiole.**

*Herbert G. Wilson, Am. J. Anat., 30:267, May 15, 1922.*

The author's material consisted of portions of the lungs of two individuals obtained soon after death, one from a woman of 30 years and the other from a child about 13 years old. In the case of the adult portions of suitable size were taken from the lungs and immersed in Bouin's fluid, but with the child's lung the entire organ was first injected through the bronchus under gentle pressure with Bouin's fluid, and then immersed in the same fluid, portions suitable for sectioning being taken only after the tissue had been fixed in this manner. The portions selected were carried through the various grades of alcohol and imbedded in paraffin; and to secure satisfactory penetration of the paraffin they were, while in 70% alcohol, placed under the bell-jar of an air-pump and the air exhausted till bubbles ceased to rise from the cut surface of the tissue. The tissue was cut in serial sections and stained with Weigert's elastic tissue stain. Wax reconstructions of the air spaces, i e. negative reconstructions of portions of each lung, were made at a magnification of 100. A study of the figures indicates that the method of branching of the bronchioles is dichotomous until the terminals are approached, and then the branching becomes irregular. Counting as the first branch a respiratory bronchiole arising from a



nonrespiratory one, the air-sac is usually reached at the fifth to seventh branch. The author found that normally there are no direct communications between adjacent alveoli, nor is there a spherical space, or "atrium," such as has been described by Miller. The bronchioles do not decrease in diameter as the periphery is approached, but remain of fairly uniform size until the air-sacs are reached, and the air-sacs are generally of greater diameter than the tubes from which they arise. Wilson observed that the lung of the child is just as complex in structure as that of the adult.

(1a—13)

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**The Formation of the Cardiac Loop in the Chick.**

*Bradley M. Patten, Am. J. Anat., 30: 373, May 15, 1922.*

The observations here recorded are confined to the period extending from the establishment of the heart as a nearly straight, double-walled tube to the period at which the process of loop formation has been completed and the main regional divisions of the heart have been definitely established. Twelve embryos ranging between 29 and 100 hours of incubation were selected as showing the characteristic steps in the formation of the cardiac loop and the early regional differentiation of the heart. Each of the 12 embryos belonging to the initial series was then carefully matched so that 3 or 4 embryos of each stage, exactly alike so far as could be determined, were available for the work. One embryo in each of these sets was reserved for study as a cleared and stained entire mount; the remaining embryos were used for dissection and serial sectioning. Camera lucida diagrams of the cephalic and cardiac regions were made from the whole-mount series. Later in the work the outlines of the heart and main vessels were completed from dissections and reconstructions of embryos of corresponding stages. The drawings of the heart shown in the plates in the article were made from dissections, principally, together with some details added from wax-plate reconstructions. The youngest stage studied is represented by embryos of 9 somites (approximately 29 hours' incubation) in which the heart is a nearly straight tube. The dorsal mesocardium at this stage forms an unbroken supporting membrane throughout the entire length of the heart. The ventral mesocardium is, however, a more transitory structure than the dorsal, and even at the 9 somite stage its rupture has begun in the midcardiac region, although its line of attachment to the heart can still be discerned. After 40 hours of incubation there is a marked dilation of the heart, but its most conspicuous change in shape is due to the bending of the entire middle portion of the heart tube to the right. In this process of bending there is undoubtedly a considerable factor of mechanical compulsion.

A graphic illustration shows how much greater is the elongation in the heart tube itself than is the increase, during the same period of time, in the distance between the attached cephalic and caudal ends of the heart. Under such growth conditions, bending of the heart is inevitable. This bending is lateral because of the impediment offered dorsally by the body of the embryo and ventrally by the yolk. Before this bending of the heart to the right has reached its maximum, torsion of the embryo's body begins to change the mechanical limitations in the cardiac region. As the cephalic part of the embryo comes to lie

on the yolk on its left side, the heart, no longer closely confined between the body of the embryo and the yolk, begins to swing somewhat ventrad and lies less closely against the dorsal body wall of the embryo. Since torsion involves the cephalic region of the embryo first and progresses caudad, the body of the embryo becomes more inclined toward the yolk at the level of the cephalic attachment of the heart than at the level of its caudal attachment. As a result, the truncus arteriosus is twisted by the carrying of its attached end away from the yolk before a similar twisting effect is exerted upon the sino-atrial region of the heart. The author believes this is the primary mechanical factor in starting the transformation of the U-shaped bend into the cardiac loop.

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**New Investigations and Considerations on the Aschoff-Tawara Node in Mammifera.**

*Domenico Pace, Riforma med., 38:386, Naples, April 24, 1922.*

Is it possible to make an histologic preparation of the Aschoff-Tawara node? Some students have answered in the affirmative; the writer holds, on the contrary, that it is impossible either to make preparations or to inject the node with India ink. For experimental and clinical needs it is sufficient to indicate as the seat of the node the terminal and the membranous cavo-atrial striae.

To what point is it possible to accompany the node from the cava to the interior of the auricle? With sections in series, the author has been able to follow the nodal tissue to its ultimate origins where it leaves the terminal furrow and penetrates into the fleshy part of the right auricle. He was not able to discover bundles of prolongation towards the Tawara node.

Is it possible to speak of the duplication of this node after the manner of Schrumpf? The latter, following electrocardiographic examination in an unusual case in which each of the auricles beat a rhythm of its own, postulated the existence of a second node of the breast, which he thought was located in the left side. Pace holds that to explain the anomaly in the synchronism of the contractions of the two auricles it is not necessary to suppose the existence of 2 nodes, but rather that, in consequence of pathologic changes of a single auricle, or of both, the stimulation starting from the node, instead of communicating itself in the normal way, contemporaneously to both auricles, finding this difficult, either induces one auricle to contract twice, or else one to contract before the other; if, then, there should cease to be any action of the node, the 2 auricles might be expected to beat, each one in a rhythm of its own, as in the case of Schrumpf.

Does the interauricular bundle of Bachmann exist? This is a muscular bundle described by Bachmann in the heart of dogs; starting from Keith's node it is supposed to spread in fan shape just to the external face of the left auricle, finishing in the extremity of the left auricular appendix. The author has been able to show that the bundle of Bachmann is not composed of special tissue, like that of Aschoff-Tawara's node, and cannot therefore be a node of conduction.

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**Anatomic Studies of the Coronary Arteries and Experimental Examination of Their Permeability.**

*A. Crainicianu, Virchow's Arch. f. path. Anat., etc., 238: 1, Berlin, April 22, 1922.*

This is a report of 3 years' anatomic and experimental study of the coronary arteries of mammalian hearts and 200 human hearts at every age with the following objects in view: (1) accurate details of the descriptive and topographic anatomy of the coronary arteries; (2) a study of the blood supply of the conducting system; (3) a study of the anastomoses of the coronary arteries; (4) a search for a precise experimental method which would show postmortem the status and value of the coronary circulation in a normal or pathologic heart.

*Descriptive Anatomy of the Coronary Arteries.*—These originate in the right and left aortic sinuses, generally at the level of the free edge of the valve, but also in a great number of cases as much as 1 cm. below it, and in a few cases above it. This fact, that the coronary arteries are generally covered by the semilunar valve, gave rise to a discussion which lasted for centuries as to whether the coronary vessels filled in systole or diastole of the ventricle, and which has now been decided in favor of the diastolic theory. In the great majority of cases there are 2 coronary arteries. In a few cases there are coronary branches springing directly from the aorta; the term accessory coronary arteries is rejected. The left coronary artery is the short vessel trunk extending from the aorta to the upper end of the anterior interven-tricular sulcus; it is 8-10 mm., rarely 20 mm. long. It sends arterioles into the posterior side of the aorta, often only a single interaortico-pulmonary artery; this anastomoses with an analogous branch of the right coronary artery, and it also sends branches to the left auricle. The chief trunk of the left coronary artery divides as trifurcate, bifurcate or quadrifurcate. In the trifurcate type an anterior descending ramus, accompanied by 2 veins and lymph-vessels, runs into the inter-ventricular sulcus, generally quite superficially, and ends in the posterior longitudinal sulcus, passing around the apex of the heart in 75% of cases; it ends on an average 15-20 mm. from the apex of the heart. The second chief branch of the trifurcated anterior coronary artery is the circumflex branch which passes off almost perpendicularly from the origin of the descending branch. It runs in the left atrioventricular sulcus, partly covered by the left auricle, and its development is in inverse proportion to that of the right coronary artery. In the bifurcate type of division, the diagonal artery is lacking as an independent branch; a side branch corresponding to it springs from one of the 2 chief arteries. In addition to the 3 branches of the trifurcate type there is a fourth chief branch which, however, is small and runs on the anterior wall of the left ventricle. The right coronary artery runs, after it emerges at the level of the right sinus of Vlasalva, downward and outward in the right limb of the coronary sulcus to the upper part of the posterior longitudinal sinus, enters this and ends at varying distances from the apex of the heart. It has 2 types. It sends out ascending branches for the auricle, which are also of importance in supplying Keith's and Flack's nodes; a curved branch enters the septum of the

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antrium, then turns to the upper side of the right auricle and ends near the inferior vena cava. In 10% of cases, the right coronary ends on the posterior surface of the right ventricle. Then in its course between the margo acutus and the sulcus interventricularis it gives off ascending branches, then branches for the septum of the antrium (which however may also come from the left coronary), and finally branches for the posterior wall of the right ventricle, which in that case is supplied by both coronary arteries. The coronary branches which come directly out of the aorta are in reality only normal collaterals which occasionally spring directly from the aorta.

*The Conducting System.*—The Keith and Flack nodes are supplied in 3 ways: (1) from the right coronary through the interauricular artery (the most frequent way); (2) through the circumflex branch of the left coronary, the branch originating in front of or behind the left auricle and describing a long curve before it reaches the node in which it ends; (3) by the same branches, but coming from both coronaries. Tawara's nodes and His' bundle get their blood in most cases from a special branch of the right coronary, which passes through the septum of the atrium to the node, provides it abundantly with blood and ends in the 2 limbs of His' bundle. These branches may in rare instances come from the left coronary.

*Topographic Anatomy of the Coronary Arteries.*—The dissected hearts are injected with opaque solutions, and after cutting in the proper planes are studied radiographically. Gelatin solutions are used, impregnated with minium or a mixture of minium, oil and carbon disulphid, after the evaporation of which an almost rigid mass remains in the vessels. With the aid of this method, the facts observed on dissection could be verified and followed up, especially those with reference to the formation of anastomoses. The corrosion method, which was tried at first, failed completely in the study of anastomoses of the coronary arteries. The results of radiography can be utilized only with caution. But this method shows that the anastomoses are mostly very fine arteries of the size of capillaries.

*Experimental Study of the Permeability of the Coronary Arteries and the Pathogenesis of Angina Pectoris.*—Among the theories on the pathogenesis of angina pectoris, the nervous and the vascular ones are the most important and the latter has the most adherents. The relative ischemia of the myocardium brings about an attack when increased functional demands are made on it, which is transmitted also to nerve centers by the involvement of the cardiac nerves. The coronary branches are to be regarded functionally as terminal arteries, in spite of their anastomoses. But there are 2 objections to this theory: (1) cases of angina pectoris may occur without anatomic changes in the coronary arteries. This unusual finding is attributed to spasm of the coronaries. As a matter of fact, the coronary vessels are found empty of blood in patients who have died of angina pectoris after nicotin poisoning. (2) Coronary stenosis may exist without angina pectoris. In these cases by slow adaptation to the gradual vessel changes, a sufficient blood supply may be brought about through collateral vessels.

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**The Evolution of Human Races in the Light of the Hormone Theory.**

*Sir Arthur Keith, Bull. Johns Hopkins Hosp., 33: 155, May, 1922.*

In the first of his 3 Herter Lectures in 1921 Keith announced the hypothesis that the action of the glands of internal secretion play a great part in the differentiation of human races. He was first led to this view by studying in comparison with the first Neanderthal skull a modern acromegalic skull, and noting the great resemblance. As evidence for his hypothesis the rest of the lecture is spent on a description of the skulls of acromegaliacs from the standpoint of bony morphology. It is found that the acromegalic skull is formed as if it had merely continued growing past the adult stage. An influence arising from the pituitary gland leads to general overgrowth of all the bodily tissues. The muscles are mostly concerned in this, and it is their growth and increased pull which leads to skeletal changes. The changes in the skull are just those which would be expected to follow overgrowth of the muscles of mastication and the nuchal muscles. In subsequent lectures the bearing of these facts upon anthropology will be expounded.

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**The Height of the Center of Gravity in Man.**

*Marguerite I. Croskey, Percy M. Dawson, Alma C. Luessen, Irma E. Marohn and Hazel E. Wright, Am. J. Physiol., 61: 171, June 1, 1922.*

Borelli made the original investigation of the center of gravity in man by placing a naked subject in the supine position upon a plank which he adjusted over a triangular prismatic bar until equilibrium was attained. When the plank and subject were nicely balanced, a vertical plane drawn upward through the supporting edge of the prism was held to contain the center of gravity of the body. The authors have added to existing improvements in Borelli's method by having the fulcrum screwed to the plank so that the plank could be balanced once for all, and by having the surface of the plank marked off by parallel cross lines 5 cm. apart. Measurements were made by a sliding wooden scale. The subjects were tested on the see-saw in a supine position but the position of the extremities was thus varied: (1) knees and thighs flexed and soles pressed down against the plank; (2) arms extended as far above the head as possible; (3) knees drawn up and arms extended above the head. Observations made upon 50 men and women revealed a difference in the location of the center of gravity of less than 1% of the body length. It is higher in men and more variable in women. The authors found no acceptable correlation between the weight or height and the center of gravity. Extending the arms above the head raised the center of gravity more in men than in women. Flexion of the legs raised the center of gravity more in men. Such possible sources of error as clothing, meals, awkward position of the subject affected but little the results of the research. (Much of the authors' data are graphically recorded in the article.)



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**The Mechanism of the Regulation of Intra-Abdominal Pressure.**

*Helen C. Coombs, Am. J. Physiol., 61:159, June 1, 1922.*

Previous workers in this field believe that under normal conditions, with the viscera entirely filling the cavity, there is a slight positive pressure in the abdomen. Coombs, thinking that an increase in the volume of the abdominal contents should, by the accompanying variations in pressure, throw some light on the mechanism of the activity of the abdominal wall, experimented on cats under light and deep anesthesia and after decerebration. A cannula was introduced into the abdominal cavity and connected by a 3-way stopcock with a manometer and a burette filled with Ringer's solution. In many cases costal respiration was recorded throughout the experiment. Blood pressure also was taken on a large number of cats. The warmed Ringer's solution was admitted to the abdominal cavity at the rate of 10 c.c. a minute. With each increment of fluid the pressure was read from the manometer and plotted against the volume injected. A control curve was thus obtained which in about 75 cases was found to be typical. The intra-abdominal pressure did not increase greatly in proportion to volume of fluid injected until a critical pressure was reached. At this point the character of the respiration became markedly costal. Arterial blood pressure remained unaffected. Coombs thinks the lack of increase in intra-abdominal pressure, up to a certain limit, in proportion to volume of fluid introduced, may be considered to demonstrate that reflex tonicity of the abdominal musculature which is known as postural activity. The reflex nature of this mechanism is shown by the alteration of the pressure curve when any portion of the nervous mechanism involved is subjected to injury.

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**The Ionic Theory of Stimulation. III. Ionic Theory of Stimulation of Taste.**

*P. Lasareff, Pflüger's Arch. f. d. ges. Physiol., 194:293, Berlin, March 31, 1922.*

It has been proved that stimulation of the nerves, muscles, retina and Corti's organ can be explained by the ionic theory, and the same proof is now advanced for the sense of taste. In these cases Loeb's law applies, namely  $C_1 \div (C_2 + a) = K$  (constant), in which  $C_1$  and  $C_2$  indicate the concentration of the stimulating and stimulus-inhibiting ions, respectively, and  $K$  indicates a constant. The author agrees with Oehrwall that in the tongue there are different sorts of papillas for the sensations of sweet, sour, bitter and acid, each of which contains a substance sensitive for that particular taste; the substance in the papillas that are sensitive to sweet is decomposed by all kinds of sweet substances, etc. A formula has been evolved which takes into consideration the duration of action; the values calculated for 0.1, 0.07, 0.05 and 0.03 N. salt solution have been compared with the time value, that is with the time elapsing before the salty taste is noted. There was a satisfactory agreement in the results. It is of interest that the phenomena of adaptation to vision in the dark, to audition and to taste follow the same quantitative laws.

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**A Contact Pendulum for the Production of an Electric Closing of the Current for a Definite Period of Time.**

*Erich Schiff, Pflüger's Arch. f. d. ges. Physiol.*, 194:330, Berlin, March 31, 1922.

For the production of contact stimuli of about  $\frac{1}{2}$  second duration the author uses a needle pendulum hanging by a thread; on passing through the perpendicular the thread comes in contact with a metal rod of small diameter (nail), which lies perpendicular to the plane of oscillation. There is a contact between the thread (which at this place is replaced by a bundle of 12 fine copper wires) and the nail. The duration of the contact depends on the height at which the thread meets the nail, as a new pendulum is formed here, whose point of suspension is determined by the place of contact. A single oscillation is attained by an electromagnetic arrest of the body of the pendulum.

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**The Electric Conducting Properties of Mammalian Skin.**

*Martin Gildemeister, Pflüger's Arch. f. d. ges. Physiol.*, 194:323, Berlin, March 31, 1922.

The resistance of the human body to the electric current is greater than would correspond to its content in electrolytes. This has its site primarily in the skin. It has been assumed that the current penetrates through the entrances of the sweat glands, but that at other places it is stopped by the horny layer. The human skin has a series of peculiarities with reference to conduction. Resistance to the direct current seems smaller when the current is raised to a high tension and on going back to a lower tension a depression of resistance remains (hysteresis). Above a certain tension, resistance to the direct current decreases with time. Resistance to the alternating current is less than to the direct current, and does not undergo the marked variations of the latter. If the glands had any great influence, this peculiarity would not exist in the skin of the lower animals, which is relatively poor in glands. Experiments on the skin of living and freshly killed animals (dogs, rabbits, guinea-pigs) did not confirm this assumption. There were, however, certain differences. If an induction current is sent into the human skin from an induction coil with many turns, electric oscillations occur, because the polarizing capacity of the skin, together with the auto-induction of the coil, forms an oscillating system. Such oscillations occur in polarizable systems only when there is a double layer, and not when there is a diffuse electric capacity. In the human skin the double layers are very obvious; also in the dog in the internal skin of the ear and slightly in the balls of the toes, but not on the skin of the abdomen. In these places the capacity for oscillation is parallel with the density of the convoluted glands. It seems, therefore, as if the existence of demonstrable electric double layers was dependent on the convoluted glands, while the other electric characteristics of the skin of animals that are poor in glands are the same as that of man, which is rich in glands.



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**The Galvanic Skin Reflex to Sensory Stimulation in Frogs.**

*Arnt Kohlrausch and Erich Schilf, Pflüger's Arch. f. d. ges. Physiol., 194: 326, Berlin, March 31, 1922.*

Both on performing the experiments without a current and using the string galvanometer, and on using an exosomatic source of current and a rotating coil galvanometer, it was found that stimulation of curarized frogs (by striking, by cutting, by the action of light or by throwing them on the floor) after a latent period of 1-2 seconds, causes a suddenly beginning and slowly disappearing strengthening of the current conducted from outside, or of the skin current compensated to zero, just as is the case in the psychogalvanic reflex. Tactile stimuli had the most certain effect, but optical stimuli also produced the reflex. Ultra-violet light did not have any effect. The croaking of other frogs caused a weak but perceptible reflex in 6 out of 12 noncurarized frogs. This finding is of importance, in view of the uncertainty of our knowledge of the frog's capacity for hearing. The reflex occurs from an action on the skin glands. Evidently stimuli that announce danger (touching, shaking) have a strong action on the gland innervation of the frog, but harmless stimuli, such as the croaking of other frogs, have a weak effect or none at all.

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**The Effect of Temperature on the Phototropic Response of Necturus.**

*William H. Cole, J. Gen. Physiol., 4: 569, May 20, 1922.*

Previous observers have shown that *Necturus maculosus* is negatively phototropic. The animal always avoids sunlight in its natural environment as well as in the laboratory. The conclusion is that the skin is the important receptor for the photic stimulus since eyeless animals behave similarly to normal ones. The experiments here reported were performed to determine the effect on the reaction time of variations of the temperature in normal and eyeless animals. The animals were kept in a large aquarium with running water at 20° C., being thus adapted to light of very low intensity and to a medium temperature. The animals were tested singly in a dark room, where the temperature and the light intensity could be easily controlled. They were placed in a rectangular blackened dish and allowed fifteen minutes for acclimatization. At the beginning of each trial the animal was oriented in the center of the dish, with the longitudinal axes of the animal and the dish parallel. A Mazda glower was fixed above so that a beam of light 10 cm. in diameter centered on the head. When the glower was turned on, the animal crawled posteriorly until the head was out of the beam of light. This interval was designated the reaction time. Four intensities of light were used at four different temperatures (2°, 12°, 22°, and 32° C., respectively). Six animals were similarly tested after the eyes had been removed. Since the averages obtained were almost identical with those from normal animals the author concludes that the skin is the important receptor for the photic stimulus.

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**Kinetics of the Bioluminescent Reaction in Cypridina. I.**

*William R. Amberson, J. Gen. Physiol., 5:517, May 20, 1922.*

Amberson has made an attempt to discover some of the time relations involved in bioluminescent reactions, specifically to study the rate of decay of the light produced when aqueous solutions of enzyme and substrate are added together. This paper deals with a photographic method which has been developed for this study, and with the results which it indicates. The material employed was the Japanese ostracod, *Cypridina hilgendorffii* Müller. The Cypridinae were dried, powdered and ether extracted. Aqueous solutions of the enzyme, luciferase, were prepared by extracting Cypridina powder with cold water until the luciferin was completely oxidized and light ceased to appear. Luciferin solutions were prepared fresh for each experiment by the extraction of a sample of about 2 gm. dry powder with about 40 c.c. boiling water.

In the author's photographic method he used Eastman cine-negative motion picture film, obtained before perforation so that the whole width of the film was available for use. He then constructed an optical system which would focus the light given out by the reaction upon the moving film. For this purpose a simple test-tube container to the side of which was cemented a phosphor-bronze strip in which a vertical slit window had been cut, was employed. The two slit windows were cut in the phosphor-bronze strips by a milling machine to a width of 1.5 mm. and a height of 6 mm. The apparatus was so adjusted that light could pass from the containers only through the slit windows themselves. The two containers were clamped upon uprights and brought close to the drum of a Zimmermann kymograph. They were adjusted for each experiment so that the line connecting container center and drum center passed through the middle of the slit window, giving a symmetrical and identical orientation for both containers with respect to the drum. The containers were placed side by side, one of them being fixed about 10 mm. higher than the other. Records were taken in a dark room. A length of film is wound tightly about the drum, firmly fastened, and then revolved past the slit windows, where it is affected by light issuing from the reacting solutions placed within the two containers. Records are thus taken simultaneously. The containers are brought to a standard distance of 1 mm. from the surface of the drum and when they are correctly adjusted, and the film applied to the drum, aqueous luciferin solutions (20 c.c. to each container) are measured out with a pipette. Pressure upon a bulb throws into each solution, at the proper instant, while the drum is in rotation, 1 c.c. of luciferase. For the evaluation of photographic records produced by unknown light intensities it is important that the calibration exposures should be produced by light of exactly the same quality.

The author made use of the Cypridina light itself for the impressing of calibration exposures. Two-thirds of the width of the film strips are given over to the moving records. Upon the other third there is impressed a series of 15 calibration exposures. Fifteen calibration exposures were impressed simultaneously through a series of 15 windows in which were placed neutral photographic filters of various known transmission values. Measurement by the pyrometer (an apparatus illustrated and described in great detail in the article) showed

that the filters used were very nearly neutral throughout that region in which Cypridina light affects the film. This method has proven a rapid and satisfactory way of impressing calibration exposures which upon development give a series of densities whose corresponding previously incident relative intensities are accurately known. From these values a curve of blackening is drawn for each experiment, and densities read along the moving records are referred to a standard curve for evaluation.

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**Kinetics of the Bioluminescent Reaction in Cypridina. II.**

*William R. Amberson, J. Gen. Physiol., 4: 535, May 20, 1922.*

Amberson has plotted the decay curve of luminescence in Cypridina. The abscissae represent time in millimeters along the film; the ordinates, intensity of luminescence. The chart also contains a slanting line for which the abscissae represent time and the ordinates the logarithm of intensity. This decay curve of the light produced in the course of the luminescent reaction in Cypridina is, after the first second, in complete agreement with the theoretical expectation for a monomolecular reaction, if light intensity at any instant is assumed to be proportional to reaction velocity at that instant. The first second or two of the reaction is characterized by a brilliant initial flash, produced at the instant of the union of luciferase and luciferin solutions. The value of the flash is much too high to accord with succeeding intensities. The significance of this flash is problematical but the author suggests that this initial high reaction velocity is an indication of a heterogeneous system. He also observed that identical solutions run simultaneously gave decay curves which checked within the limits of the photographic error. Stirring did not affect the reaction velocity or the form of the decay curve. Reaction velocity was found to be proportional to enzyme concentration over the range of concentrations used in this study.

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**The Structure of Heart Muscle Fibers.**

*K. Hürthle and K. Wachholder, Pflüger's Arch. f. d. ges. Physiol., 194: 333, Berlin, April 20, 1922.*

By the use of Skramlik's preparation it is possible to isolate thin muscle bundles with parallel fibers in the third of the auricle of the frog's heart which is adjacent to the auriculoventricular boundary; in these bundles it is possible to observe directly the process of contraction in the living muscle fiber. Microphotographs were made of the individual phases. During diastole the musculature of the isolated auricle contracting regularly in Ringer's solution shows symmetrical transverse segmentation by the alteration of single and double refracting elements. Z-stripes were not observed. The height of the muscle cells was on an average 2.2-2.8 microns in diastole, occasionally, as a result of greater dilatation, 4 microns. When the contraction continues the transverse striation may sometimes become not very well defined or

may even disappear. It has not yet been possible to make accurate observations during systole first on account of the slight injury of the fibers and second on account of the shortness of the systolic contraction.

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**Studies on the Origin and Conduction of the Cardiac Impulse.  
VIII. The Permanent Rhythm Following Destruction of the Sino-Auricular Node.**

*J. A. E. Eyster and Walter J. Meek, Am. J. Physiol., 61:117, June 1, 1922.*

The authors undertook this research to determine the late effects of sino-auricular node ablation and the type of final or permanent rhythm established, as well as the relation of the auriculoventricular node to chronotropic vagus control. Dogs were used in all the experiments. Electrocardiograms were obtained for 2 or 3 days previous to the operation on the node and in certain cases the influence of exercise and of atropinization as controls on the normal animal were also studied. The normal resting heart rate and auriculoventricular interval (P R electrocardiographic interval) were thus obtained. The animals were then operated upon; in seven of them the sino-auricular node was tied off from the surrounding auricular and caval regions by a series of ligatures. In 10 animals the node was first isolated by a series of mattress sutures and then excised. Of 17 animals operated upon 14 survived. Determination of the seat of impulse origin was made in 12 at periods from 48 hours to 97 days by opening the thorax under artificial respiration and ether anesthesia and finding the seat of initial negativity by means of pairs of electrodes connected to the string galvanometer. Points in the sulcus above and below the excised region, the right auricle, caval region, coronary sinus and the main portion of the auriculoventricular node were compared in the manner previously described by the authors. In the last 7 experiments the tissue excised was sectioned and examined histologically to determine the amount of nodal tissue removed. At the death of the animal a block of tissue surrounding the area of excision was also saved, so that if all of the node could not be identified in the tissue originally removed, examination of the surrounding tissue would give information as to the amount of nodal tissue remaining.

The results demonstrate that following ligation or excision of the sino-auricular node in dogs, disturbance of the normal rhythm, as manifested by a reduction in cardiac rate, a reduction in the As-Vs interval and frequently other changes, invariably result. In the ligation experiments, recovery of the normal rhythm may ultimately occur after a prolonged period of auriculoventricular or coronary sinus rhythm, and in some cases after a period of partial sino-auricular block. After complete or nearly complete excision of the node the final permanent rhythm arises from the coronary sinus region, probably from the auricular portion of the auriculoventricular node. The development of coronary sinus rhythm was in most cases preceded by a period in which the dominant rhythm arises from the ventricular or main portion of the auriculoventricular node. Control experiments in which similar operative procedure was carried out and a segment of the right atrium

near the sino-auricular node was excised, were without effect on the cardiac rhythm. These facts substantiate the paramount importance of the sino-auricular node as the seat of origin of the cardiac impulse in the normal animal and also indicate the ability of this structure to function, even though subject to considerable injury and partial isolation, if sufficient time for recovery is allowed. A study of the cardiac acceleration, preceded by muscular exercise and by vagus paralysis under atropin administration, before and after excision of the sino-auricular node, and in animals in auriculoventricular and in coronary sinus rhythm, indicates that the vagus exerts a greater chronotropic control upon the coronary sinus region than upon the main portion of the auriculoventricular node. The influence of the vagus in the control of automaticity is greatest upon the sino-auricular node, next upon the auricular portion of auriculoventricular node and next upon the ventricular portion of this latter node.

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**Experiments on the Origin and Conduction of the Heart Beat.**  
**IX. Sinoventricular Conduction.**

*J. A. E. Eyster and Walter J. Meek, Am. J. Physiol., 61:130, June 1, 1922.*

The authors review their work already published regarding conduction of the cardiac excitation from the sino-auricular node to the right auricle and auriculoventricular node. By means of an indifferent electrode on some part of the body of the dog and another electrode placed successively on the sino-auricular node, auricle and auriculoventricular node, and connected with a string galvanometer, the time at which electronegativity developed in each of these regions was compared with the mechanical systole of the right auricle. The excitation was found to reach the auriculoventricular node and the right atrium at approximately the same time. Direct comparisons of the sino-auricular node with the surrounding parts indicated a more rapid spread of the excitation toward the venous and intercaval regions surrounding the node than toward the right atrium.

The further evidence for sinoventricular conduction presented in this article was obtained in the dog from experiments in which the sino-auricular node was partially isolated by ligation and the animals allowed to recover. The authors believe this evidence strongly supports the hypothesis of conduction from the sino-auricular node to the auriculoventricular node independently of the right atrium. When sino-auricular rhythm was reestablished in the dogs, conduction to the auricle was sufficiently normal to occur with every sinus impulse, but conduction to the ventricle was below normal and only approximately every other beat, arising within the sino-auricular node, was conducted to the ventricles. The conclusion that the auriculoventricular dissociation noted in these experiments was due to injury to the path of conduction between the sino-auricular and auriculoventricular nodes and that furthermore the path of conduction between the sino-auriculo node and the auricles was not seriously interfered with, the authors believe is justified by the experimental facts and adds further evidence pointing to the presence of these two separate paths of conduction. They regard the condition in these experiments as that of true sinoventricular block.

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**Preliminary Report on Experiments on the Rôle of Electrolytes in the Heart Beat, the Effect of Salt in Hemorrhage and the So-Called Tonus Current.**

*F. Kraus and S. G. Zondek, Klin. Wchnschr., 1:996, Berlin, May 13, 1922.*

If an isolated frog's heart is nourished with Ringer's solution the potassium content of which is increased, the contraction of the ventricular muscle decreases in strength until the heart is arrested in diastole. With increased calcium content the contraction increases in strength until systolic arrest. If at the height of its action the nutritive solution of the heart is tested for its content in  $H^+$  and  $OH^-$ , it is found that in the potassium heart there is an increase of  $OH^-$ , in the calcium heart an increase of  $H^+$ . Neutral red is used as an indicator and rosolic acid for the demonstration of acidity. The potassium solution becomes more alkaline, the calcium solution more acid. Ringer's solution with atropin acts like a solution rich in calcium. The observed difference of reaction is undoubtedly the true cause of the antagonism between ions acting like calcium ions and those acting like potassium ions.

After a rabbit has been bled from the carotid until the blood pressure sinks to zero and the heart beat can no longer be heard, if 1 c.c. of salt solution is injected into the jugular vein, followed by a second and possibly a third injection, respiration and heart action will begin before the blood pressure has risen enough to nourish the heart. If this experiment is repeated in a rabbit with sectioned vagus and sympathetic nerves on both sides and upper cervical cord, the blood pressure is not restored after the infusion of 30 c.c. of salt solution, and the circulation is maintained only by the restored heart beat. From this it appears that certain tissues can actively take possession of the cations of the blood. In a spinal cord specimen, stimulation of the central stump of the sciatic nerve produces a reflex muscle twitching, which on the string galvanometer shows only the diphasic action current. If in addition to the spinal cord the medulla and the corpora quadrigemina are left intact, a long-continued contraction follows the same stimulus. This shows the action current and the tonus current, consisting of 2 phasic parts. In calcium animals the tonus current is especially characteristic.

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**Studies of the Conduction of the Action Current of the Heart from the Thorax.**

*Fritz Schellong, Ztschr. f. d. ges. exper. Med., 27:115, Berlin, March 25, 1922.*

Drury and Iliescu have examined cases of auricular fibrillation electrocardiographically by conduction from the thorax. Schellong examined normal and pathologic cases by this method. Copper plates 4-5 cm. in diameter can be fastened with a paste to the damp skin at the insertions of the second right rib and the seventh right costal cartilage, or to the middle of the sternum 6 cm. to the right of the spinal column at the level of the angle of the scapula. The first sort of conduction proved the more favorable. The conductions described are not affected

by tremors, which otherwise would be unavoidable, as for instance in paralysis agitans. Simultaneous recording of the second conduction showed the superiority of the conduction from the thorax in the delineation of the P peak. One case of auricular fibrillation could be demonstrated only by thorax conduction. On the other hand the author saw cases in which thorax conduction did not show any P peak while the second conduction showed a normal picture.

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**Analysis of the Change in the Heart Rate Following a Rise in Temperature.**

*Peter Gillessen, Pflüger's Arch. f. d. ges. Physiol., 194:298, Berlin, March 31, 1922.*

In experiments on rabbits it was found that when the whole body was heated the increased pulse rate is preceded by a temporary marked fall. Hürthle's tonometer, connected with the left carotid, was used for registering the pulse. The temperature was measured once in the rectum and then in the mediastinum by means of a thermometer introduced along the esophagus. The temperature was raised by applying hot water to the skin, dipping the ears in hot water and heating the blood in a cannula which connected the right carotid with the right jugular vein. Immediately after the application of the heat, when the animal is quite quiet, there is a slowing of the pulse for a few seconds. This does not occur after atropin injection. A less pronounced slowing of the pulse can be brought about by purely sensory stimuli (striking or pressing on the ear). But skin stimuli are excluded in the use of the cannula and direct heating of the blood. In this form of the experiment there is a primary increase in pulse rate which lasts a few seconds, and then a slowing of the pulse which lasts for 10-30 seconds, and is never so great as to fall below the original pulse frequency; finally a secondary increase in pulse rate occurs which lasts until the heat is discontinued. In these cases, too, the slowing of the pulse does not occur after atropin or cutting the vagus nerve. Direct heating of the carotid blood passing to the brain, by means of a U-shaped cannula introduced into the carotid, does not cause any marked slowing of the pulse if the temperature is not raised to so high a degree as to heat the animal's whole body. This is therefore to be regarded as due to a reflex stimulation of the vagus. As the primary increase in rate is not affected either in the quickness with which it appears or in the frequency attained, by exclusion of the vagus nerve, it is to be regarded as the result of a direct action of the rise of temperature on the areas where stimuli are developed in the heart.

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**The Effect of Cooling on the Heart Rate in Warm-Blooded Animals.**

*Andreas Hachenberg, Pflüger's Arch. f. d. ges. Physiol., 195:308, Berlin, March 31, 1922.*

Both carotids, the right jugular vein and sometimes the right and left femoral arteries of rabbits were dissected out. The temperature was measured in the rectum and mediastinum and the pulse of the left carotid

taken by means of a tonometer. The cooling was accomplished by dipping the ears in a cold fluid, from 8-10° C. or from 1-3° C., by laying an ice-bag on the abdomen and thorax, by direct cooling of the carotid by placing a cold mantel around it, or by introducing a U-shaped cannula between the carotid and jugular or into the course of the carotid. Independent of the nature of the cooling there was first an increase in pulse frequency, which on further cooling gave way to a progressive slowing of the pulse. If the temperature of the rabbit falls below 37.5° C., bilateral section of the vagi does not cause any marked increase in pulse beat, and if vagotomy is performed before cooling, the increase of pulse caused by the cooling does not occur. Therefore the absence of the increase in pulse after vagotomy, in animals cooled to less than 37.5° C., is to be attributed to a decrease in vagus tonus. The secondary slowing of the pulse on cooling is probably dependent directly on the areas of stimulation in the heart and not on a central stimulation of the vagus. Section of the vagus at this period in the experiment does not have any effect on heart frequency. Direct cooling of the blood flowing into the heart through the arteriovenous cannula with the vagi intact causes a primary slowing of the pulse by direct action on the cardiac stimulating areas, and secondarily after about 30 seconds a quickening of the pulse from decreased vagus tonus and finally a permanent slowing as a result of the continued action of cold in the stimulus-forming areas in the heart. If the vagi are excluded before the experiment, only the latter slowing of the pulse occurs. A decrease in stimulability of the cardiac vagus can only be observed below about 24° C.

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**The Blood Flow in Man as Estimated by the Calorimetric Method of Stewart.**

*N. B. Taylor, J. Lab. & Clin. Med., 7:439, May, 1922.*

With certain minor modifications in the method, experiments were made upon normal subjects of both sexes, of ages varying from 20-35 years. In the majority of the cases, observations were made simultaneously upon the two hands, readings being taken every minute for periods of 10 minutes. From a large number of blood-flow determinations upon normal individuals it has been found that the amplitude of the flow differs widely in different persons; that the flow fluctuates spontaneously to the extent of several grams per 100 c.c. per minute in the same individual during the course of an experiment; and that marked alterations in the flow are affected by changes in the temperature of the atmosphere. The flow in the hand may be influenced reflexly by applications of heat or cold to either hand or foot. Thus, immersion of the hand in hot or cold water produces a rise or fall respectively in both hands. The response to draughts is similar in nature to the response following the immersion of the hand in cold water. Heat applied to the feet produces in some individuals a rise and in other a fall in the blood flow through the hands; the particular effect produced is constant for the same individuals. Local exercise produces a drop in flow of the opposite hand, the flow in the exercised hand being increased in some cases and reduced in others.



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**The Mean Arterial Flow of Blood in Man as a Function of the Radius of the Vessel.**

*R. Thoma, Pflüger's Arch. f. d. ges. Physiol., 194:384, Berlin, April 20, 1922.*

On the basis of careful measurements of arteries injected with paraffin the author obtained, by the use of a method previously described, numerical data on the mean quantitative flow in the different arteries. The mean flow in the ascending aorta is 82,500 cu. mm. per second. The mean flow seems to be a function of the radius. The behavior of the plasmatic marginal zone of the blood current must be taken into consideration as well as the existence and significance of a coefficient of gliding  $\xi = \frac{\theta}{\epsilon}$  in which  $\theta$  is the coefficient of the internal friction of the blood plasma and  $\epsilon$  the external friction of the blood stream. It was found that the rapidity of the blood current in the marginal zone of the different arteries is by no means equal, but rises rapidly in the smaller arteries. Depending on whether it is assumed that the outer surface of the plasmatic marginal zone adheres to the vessel wall or glides along it, the rapidity of the current  $s$  on the surface of the red axial current or the rapidity  $\tau$  on the inner surface of the artery, is determined by equations of the formula  $a \div b (11.2 - R)^2$  mm. sec., in which  $a$  and  $b$  are constants (naturally differing somewhat in the two cases),  $R$  is the radius of the blood vessel under consideration. No exact proof of the existence of a coefficient of gliding  $\xi$ , has been advanced; if it exists it can hardly be greater than 0.006. At any rate many findings indicate the existence of a coefficient of gliding and if this is assumed, it is much easier to reconcile the calculated values with those found. This would indicate that the plasmatic marginal zone glides on the arterial wall. This is the only way in which it is possible to explain the amount of flow in the large arteries and the great rapidity in the small arteries. The author assumes that the arterial wall feels the rapidity of the blood current and reacts to this unconscious sensation with a positive or negative change in circumference, until that rapidity of the marginal zone is attained which corresponds to the vessel radius. The form of the equations for  $s$  and  $\tau$  seems therefore to indicate that Fechner's law holds for unconscious sensations.

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**The Effect of Mountain Climate upon the Capillary Circulation and the Relation of the Latter to the Increase of Blood Corpuscles and of Hemoglobin Observed in High Altitudes.**

*Paul Liebesny, Schweiz. med. Wchnschr., 52:431, Basel, May 4, 1922.*

The effect of mountain climate, and the cause and mechanism of this effect have not yet been explained. The theory of Zuntz, which assumes an accumulation of blood-corpuscles in the capillaries, and Bunge's theory of the constriction of the vascular system have not been subjected to special study. The author endeavored to decide this question by observing the capillaries with the skin microscope. The observation of the capillaries in healthy persons in the high districts (170 m.)

around Vienna shows that the parallel capillary legs are almost equally thick, so that the venous and arterial branches can be differentiated only by the direction of the current. Under normal conditions the circulation cannot be seen or only slightly, but it becomes distinct when the homogeneity of the circulation is disturbed, when the current becomes "granular." At St. Moritz (1800 m.) it was observed that the circulation is retarded and a finely granular or coarsely granular circulation was found residing there only a short time. At moderately high altitudes (461 m.) the capillaries generally showed a homogeneous filling and only rarely granular filling. In an excursion from Vienna to Schneeberg (1800 m.) a retarded and granular circulation was observed in 8 persons examined after a short stay at the latter place; in 6 persons there was such an accumulation of erythrocytes in one part of the capillaries that the capillary wall appeared irregularly sinuous. The sudden effect of the mountain climate leads to capillary varices, which disappear, however, after a sojourn of several days at the high altitude.

These observations substantiate the Zuntz theory of altered distribution of the blood-corpuscles under the effect of altitude. On the other hand, the clumping of the erythrocytes in the capillaries can be brought in accord with Bunge's theory of constriction of the vessels with expression of plasma. Both theories assume that the increase of blood-corpuscles is relative. The marked accumulation of the blood-corpuscles in the capillaries probably explains the pronounced increase of corpuscles in all persons examined immediately after reaching a high altitude. It is still unknown what factors of the mountain climate are responsible for the changes in the capillary circulation.

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**The Functional Characteristics of the Blood-Vessels of Isolated Normal and Pathologic Organs of Animals and Man.**

*N. P. Krakow, Ztschr. f. d. ges. exper. Med., 27:127, Berlin, April 8, 1922.*

The method of Laewen-Trendelenburg (perfusion of the hind legs of the frog with Ringer's solution) has the disadvantage of developing an extreme edema. This is due to the fact that in preparation the sciatic vein has to be ligated, so that only the abdominal vein remains to carry the blood away, while blood is being supplied in normal amount by the aorta. Therefore Pissemsky left all the veins open. The nutritive solution flows out through all the sectioned veins, in an amount proportional as to time to the width of the vessels. But in experiments with toxins it was found very difficult to flush them out. Nor can results obtained in cold-blooded animals be applied unconditionally to warm-blooded ones. A second method was devised by Frey and Meyer. Rings were cut out of the larger vessels, opened out flat, and each strip immobilized in Ringer's solution at one end and at the other connected with a kymograph which registered all contractions of the strip. This method is unphysiologic, as the vessel elements are cut, and so do not have a normal tonus and are not reached by the toxins in a normal way, through the vasa vasorum.

Perfusion of the isolated rabbit's ear has great advantages in comparison with this method. The rabbit's ear is supplied with blood by the auricular artery. It is not necessary to tie a cannula into the auri-

cular vein. The vessels of the rabbit's ear, if kept cold, remain capable of functioning. The human finger, too, is very well adapted to the study of the peripheral vessels, as there is no muscle tissue present. The vessels of this preparation also keep their reactive capacity for a long time. Moreover, the vitality of the finger manifests itself by the growth of the nail or the production of sweat which can be brought about by the perfusion of a pilocarpin solution. Perfusion experiments were also made with rabbit and human hearts. The heart was brought to a standstill with strophanthin. When this had occurred it could not be made to beat again with adrenalin, while the vessels remained stimuable. The functional activity of the coronary arteries of the isolated organ depends essentially on the heart disease that had existed during life. The most difficult function to reawaken is the activity of the left ventricle of adults; contractions of the auricles are most frequently seen.

If rabbits' ears, before being severed, were dipped in water at 54° C. for 3 minutes to produce inflammation, or rubbed with croton oil, the vessels of the inflamed ear contracted less to adrenalin (which in this case even causes dilatation after a brief contraction), cocain and histamin. Caffein caused a more pronounced dilatation than in the normal ear. In observing the Ringer's solution flowing from the vessels, Krakow noted periodic variations in its amount. This was much more pronounced when the tips of the ears were cut off, so that the nutritive solution only had to pass the arteries. Under this condition periodic automatic contractions of the arteries were observed. The duration of a contraction was 5 to 10 minutes. Ten days after the isolation, such rhythmic contractions were still observed in the rabbit's ear. The contractions were strengthened by adrenalin, histamin, ergotin, pituitrin, nicotin, strychnin, blood serum and suprarenal extract of rabbit. Veratrin weakened the contractions. The substances which exist normally in the organism have the strongest action. The heart stimulants, digitalin and strophanthin, were also powerful stimulants of rhythmic vessel contraction. The rhythmic contractions caused by adrenalin stopped under the action of atropin (1:10,000).

Essentially the same results were obtained with the isolated human finger. The rhythmic contractions of the blood-vessels do not really act as a peripheral heart, but as a sort of massage in furthering the onward movement of the blood. Therefore the presence of adrenalin and the like in the blood would play a part in the circulation. The action of heart stimulants can also be appreciated from the point of view of the action of the vessels.

When attempts were made to produce rhythmic contractions in the vessels of the inflamed isolated ear with adrenalin, they not only failed, but it was found that adrenalin causes a dilatation instead of a contraction of the vessels. Automatic rhythmic contractions cannot be produced in the rabbit's ear when the inflammation is pronounced. Krakow succeeded in producing inflammation in the already isolated ear by rubbing it with croton oil. There was at first marked dilatation of the vessels, in which the independent rhythm was preserved but irregular. When edema begins and the fluid discharged decreases, the stage arrives when adrenalin no longer has any action, or causes a dilatation, and the rhythmic contractions stop. These are the same phenomena that occur in the ear that is inflamed *intra vitam*.

Three methods may be used to keep the isolated rabbit's ear and human finger capable of reaction for a longer time. The isolated organ may be: (1) placed on paraffin with the cut surface down; or (2) mummified in an exsiccator; or (3) kept with the cut surface down in a cylinder over chloroform. Mummified fingers were brought to the consistency of a cadaver's finger before the experiments, by the use of water vapor and chloroform. The fingers kept in paraffin or water vapor atmosphere at room temperature always had a temperature that was higher by  $1^{\circ}$ — $1.5^{\circ}$ C. than the surrounding temperature. The nails grew in 1-2 months 1.5 mm. The reactive capacity of the peripheral vessels could be preserved for 6 months.

Perfusion experiments were also made with human hearts isolated several hours after death. If, on the principle of Langendorff's method, an insufficiency of the aortic valve was found, the cannula was put directly into the coronary artery. Hearts of fetuses and children began to beat sooner than those of adults. In the latter, the first contractions occurred in the auricle at the mouth of the superior vena cava. These contractions could be strengthened by adrenalin or caffeine. The purpose of the experiments was to observe the coronary vessels. They showed that the coronary arteries of man react in the same way to toxins as do those of animals, except that in the former the action of the vasoconstrictors is less intense. It is an interesting point that adrenalin, which has no effect on the coronary vessels of fetuses and children, or even dilates them, constricts the vessels of adults.

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**The Relations between Mastication and the Motility of the Stomach Based on Physiologic Experiments.**

*Leo Lührse, Pflüger's Arch. f. d. ges. Physiol., 194:109, Berlin, March 24, 1922.*

If it is desired to test the effect of mastication alone on stomach motility without the effect of secretion, something must be given that will not stimulate secretion, i. e., water. This should be introduced through a sound without mastication. In the experiments recorded the motility was examined through a duodenal fistula in a dog. The water contained methylene blue. Mastication was done with nothing in the mouth, or the animals chewed on hard pieces of wood or meat that had been dried in the air, so that they could not bite off and swallow more than very small bits. It was found that mastication had no effect on the motility of the stomach, which is under the control of the sympathetic and parasympathetic. Physiologic stimulation of the fibers of the trifacial, glossopharyngeal and olfactory, does have an influence on the gastric secretory fibers of the vagus but not on the motor fibers. Probably the chief importance of mastication lies in its stimulation of the secretory fibers of the vagus.

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**The Effect of Stratification of the Stomach Contents on the Digestion of Carbohydrates and Proteins.**

*Emil Abderhalden and Ernst Wertheimer, Pflüger's Arch. f. d. ges. Physiol., 194:168, Berlin, March 24, 1922.*

Experiments were made to determine whether a disturbance of  
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the stratification of the individual parts of the meal in the stomach had any effect on the extent of carbohydrate and protein digestion in the stomach. For this purpose observations were made of the digestive processes in the stomachs of guinea-pigs which had been given different colored foods, one after another. Some of the animals were made to jump about after taking the food; the movement more or less completely upset the stratification. In the animals which had not moved there was more amino-nitrogen in the stomach contents than in the ones that had moved, and carbohydrate digestion, as measured by the reducing capacity of the stomach contents, was greater. In rabbits also the carbohydrate digestion in the resting animals was 5 to 15% greater than in the ones that had moved. That there is a real disturbance of carbohydrate digestion cannot be assumed, for this may easily be made up in the intestine by the pancreatic and intestinal juices. Experiments on the effect of pilocarpin and cholin or acetylcholin showed that the former causes an active convulsive movement while the latter actively stimulates gastric and intestinal movements, but only influences it quantitatively and to a limited degree. Acetylcholin which is more active than cholin, in comparison with the action of pilocarpin, only causes regular movements.

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**The Physiologic Rôle of the Intestinal Mucosal Movements.**

*C. E. King, Lloyd Arnold and Jas. G. Church, Am. J. Physiol., 61:80, June 1, 1922.*

Observations were made on the villi and mucosal movements in a series of 80 dogs. By noting the general condition of the animal, blood pressure, color of the tissue, presence or absence of food, and time of previous feeding, the activity and reactivity of the mucosa can be fairly well predicted. The mucosa of animals recently fed shows greater activity and reactivity than that of starved animals, and as a rule also the vascularity is increased. Ligation of the mesenteric veins leading from the field of observation produces vigorous activity of both the villi and the mucosa for a few minutes, and then a gradual diminution and cessation. Ligation of the mesenteric arteries supplying the observed segment gives the same general results as ligation of the veins. An abrupt and marked fall of blood pressure is followed by an increased activity and then by a diminution. The activity of the mucosa is augmented by the injection of 0.02 n. acid in saline solution and also 2.5 % sodium bicarbonate, the latter being more active than the former. Concerning the relation of lymph flow to mucosal motor activity, it was found that mucosal movements, particularly those of the individual villi, are connected with the lymph flow, for it was observed that an increase in intralymphatic pressure and also the intravenous administration of lymphagogues augmented the activity of the villi.

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**The Action of Normal Serum and the Serum of Asphyxia on the Isolated Intestine.**

*Rinaldo Pellegrini, J. de physiol. et de path gén., 20:14, no. 1, Paris, 1922.*

From a well-nourished rabbit a piece of intestine about 5 cm.

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long is removed, near the duodenum. The contents are removed and the piece is placed in a tube containing about 30 c.c. Ringer's solution. Oxygen is allowed to bubble up through the solution. One end of the intestinal fragment is connected with a hook, the other with a pulley and recording device. Tube and intestine are placed in an Ostwald water incubator, with agitation provided by a screw. The temperature is kept at 39° C. Blood from the carotid artery of the rabbit is centrifuged and the serum promptly used. It may be inactive, but it often strongly increases the tonus of the intestine muscle. Serums taken from different rabbits do not behave uniformly, thus showing that they contain different amounts of the tonic substances. If the intestine which has been treated with normal serum be washed and again treated with the same quantity of the same dilution of the same serum, the reaction produced is the same as that caused by the first treatment. The serum of certain rabbits does not affect the intestinal tonus, even if tried with intestine derived from several animals. The power of the serum cannot be measured by the increase in the tonus. Several factors are involved, viz., the speed and manner of the increase, its force, and its duration.

The increase in tonus may occur rapidly or slowly, according to the quantity of tonic substances present in the serum. The duration depends on the amount of serum as well as on the tonic substances, but there is no constant relation between the intensity and duration of the increase in tonus. A serum may inhibit or stimulate the rhythmic movements of the isolated intestine. The movements increase, decline and almost disappear. There is probably no adrenalin in the carotid blood, or not enough to affect the intestine. It is very unlikely that the absence of its effects is explicable by the presence of substances which inhibit it. The serum taken from an asphyxiated rabbit may increase the intestinal tonus, with or without increasing the extent of the muscular movements, or the movements may be increased without increase in tonicity. These effects are not due to carbon dioxid. They are produced by serum obtained from animals asphyxiated by drowning as well as by exclusion of air through closure of the tracheal cannula. The effects are not due to water entering the blood. As with normal serum, they are not due to adrenalin.

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**Does the Kinetics of Trypsin Digestion Depend on the Formation of a Compound between Enzyme and Substrate?**

*John H. Northrop, J. Gen. Physiol., 4: 487, May 20, 1922.*

The author has previously shown that the inhibiting action of the products of the reaction on the trypsin is in quantitative agreement with the assumption that the enzyme and the inhibiting substance combine to form a compound which is inactive and that the rate of hydrolysis is proportional to the concentration of uncombined trypsin. He has also shown that the same assumption will account quantitatively for the protective action of the inhibiting substances when the spontaneous inactivation of the enzyme is followed. The fact that the inhibiting substance protects the enzyme from decomposition is strong evidence that the inhibiting substance combines with the enzyme. In the presence of the

substrate, however, the enzyme becomes inactivated at the same rate as the "pure" enzyme, which renders it unlikely that the enzyme is combined with the substrate. This paper contains the results of experiments planned to determine whether or not the action of the enzyme with different concentrations of substrate and of inhibiting substances can be accounted for on the assumption of a compound between the enzyme and substrate. In the experiments the rate of hydrolysis was followed by means of the change in conductivity of the solution, following the method previously described by the author. The experiments were all conducted at a pH of 6.0. The trypsin employed was a sample of Fairchild's trypsin and was purified for use by dialysis under pressure. Cooper's gelatin was used and was rendered ash-free by washing at the iso-electric point. The inhibiting solution was made by allowing trypsin to completely digest gelatin and then concentrating the solution in vacuo. To obtain a correct measure of the rate of hydrolysis it is necessary to compare the reactions at the same stage. If the reactions are compared at a point of equal percentage hydrolysis, the change in substrate concentration is corrected for, but the change in enzyme concentration will be very different. The small amount of enzyme will be inhibited to a larger extent than the large amount. If the reactions are compared after equal times, both conditions are varied. If, however, the time to cause a very small amount of hydrolysis is taken, the change in substrate concentration may be considered negligible and the effect on the enzyme will be small and nearly the same in both cases. This method, therefore, gives the most significant value. The author performed an experiment with 1 and 5% gelatin and 1 and 10 units of trypsin, and in the tabulated results plotted the increase in specific conductivity of the solution against the time in hours. It was found that the velocity of hydrolysis of gelatin by trypsin increases more slowly than the gelatin concentration and finally becomes nearly independent of the gelatin concentration. The relative velocity of hydrolysis of any two substrate concentrations is independent of the quantity of enzyme used to make the comparison. Experiments to show the influence of the viscosity of the solution, using the same gelatin solution which had been kept at 25° C. for varying lengths of time, revealed that the rate of hydrolysis is independent of the viscosity of the solution. Similarly the percentage retardation of the rate of hydrolysis by inhibiting substances was found to be independent of the substrate concentration. There is experimental evidence that the enzyme and inhibiting substance are combined to form a widely dissociated compound, but if the substrate were also combined with the enzyme, an increase in the substrate concentration should affect the equilibrium between the enzyme and the inhibiting substance. However, this is not the case. Northrup found that the rate of digestion of a mixture of casein and gelatin is equal to the sum of the rates of hydrolysis of the two substances alone. If the reaction is followed by determining directly the change in the substrate concentration, it is found that this change agrees with the law of mass action; i. e. the rate of digestion is proportional to the substrate concentration.

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**Digestibility of Raw Rice, Arrowroot, Canna, Cassava, Taro, Tree-Fern, and Potato Starches.**

*C. F. Langworthy and Harry J. Deuel, Jr., J. Biol. Chem., 52:251, May, 1922.*

The authors had previously observed that raw wheat and corn-starch, when eaten in quantity, were completely assimilated without any noted physiologic disturbances and no starch was detected in the feces. In this article they have extended the work on the digestibility of raw starches to see whether complete digestibility was characteristic of other starches and to determine whether the less complete digestibility of potato starch (78.2% on an average) was influenced by the amount eaten and also whether it was characteristic of the starch from other roots, tubers, and similar sources. The starches chosen were from rice, true arrowroot (*Maranta arundinacea*), so called commercial arrowroot (*Zamia floridana*), canna (*Canna edulis*), cassava (*Manihot utilissima*), taro root (*Caladium colocasia* or *Colocasia esculenta*), treefern (*Cibotium menziesii*), and potato. The subjects of the experiments were healthy young men and the procedure was the same as that followed in the authors' previous work. The diet was so arranged that the food-stuffs under consideration were the predominating factors, the other materials eaten being simple and having characteristics well understood. The analysis of the foods, the separation and analysis of the feces, etc., were accomplished by standard methods.

The experiments demonstrated that certain raw starches, including corn, wheat, cassava, rice and taro root were completely digested when eaten in amounts sometimes as large as 250 gm. a day. Raw treefern and true arrowroot (*Maranta arundinacea*) starches were nearly completely digested but some starch was present in the feces. Raw commercial arrowroot (*Zamia floridana*) and potato starches showed considerably less complete digestion, large quantities being present in the feces. Raw canna starch was even less digestible, its coefficient being only about 50%. In these experiments there seems to be a direct relationship between the size of the starch granules and their digestibility; whether this relationship is accidental or not has not been determined.

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**Some Human Digestion Experiments with Raw White of Egg.**

*C. G. L. Wolf, J. Biol. Chem., 52:207, May, 1922.*

In this paper the author corrects the following statement made by M. S. Rose and G. MacLeod in the January number of this Journal: "Wolf and Osterberg found in 1 case with a total intake of 23 gm. nitrogen, 70% of which was derived from raw egg-white, the loss of nitrogen in the feces was 41% of the intake; but in another period, with a total intake of 14 gm. and 51% of the nitrogen from the egg-white, the loss was only 15% of the total intake. . . ." Wolf says this is incorrect. In the second experiment alluded to where 444 gm. cooked white of egg were consumed at breakfast, the utilization was 85%, substantially the figure which these authors found in their own experi-



ment. This is quite a different experiment from the first, where 1000 c.c. of *uncoagulated* white of egg were taken at a single meal. Hence, there is no conflict between the results of the two experiments.

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**Are the Clumps of Albumin Stored in the Liver Cells Vital Preformed Structures?**

*W. Berg, Pflüger's Arch. f. d. ges. Physiol.*, 194:102, Berlin, March 24, 1922.

Berg has studied the storing of albumin in the liver cells of cold-blooded animals and rabbits in the form of irregular clumps and drops which are found in addition to fat and glycogen and are stained clear red with the methylene green pyronin mixture of Pappenheim. If the animals (*Salamandra maculata*) are not fed, these structures disappear; they reappear when the animals are fed with albumin or products of albumin catabolism (polypeptid mixture). The alcohol soluble fraction of Witte's peptone is ineffective (Cahn-Bronner) probably as the result of a toxic action. Berg and Stübel have demonstrated these structures in fixed specimens; the latter had denied their preformation on the basis of examination of fresh liver cells. But the albumin drops could also be seen in unfixed liver cells in Ringer's solution. They were not found in fasting animals. The clumps can be stained supravitaly with neutral red. They are evidently vitally preformed and only undergo certain changes through the procedures of histologic technic.

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**The Effect of Parenteral Administration of Free and Combined Purins on the Excretion of Purin Bodies in the Urine in Man.**

*A. Schittenhelm, and K. Harpuder, Ztschr. f. d. ges. exper. Med.*, 27:14, Berlin, March 25, 1922.

Schittenhelm has shown that uric acid is not an end-product of metabolism, which has been denied by other authors, because (1) no ferment has been found that catabolizes uric acid and (2) after the intravenous injection of uric acid or purin bases these appear quantitatively in the urine. In the latter series of experiments the uric acid was injected in solution with piperazin. As piperazin itself causes metabolic disturbances, and the injection of uric acid causes leukocytosis, the objection to Schittenhelm's theory of the further oxidation of uric acid is not sustained. The authors injected uric acid intravenously into subjects free of gout and found that the amount of uric acid which reappeared in the urine varied in different cases, between 18.2 and 78.8%. In a case of acromegaly the high endogenous uric acid value was striking (0.4-0.6 gm.). The subjects were given purin-free diet and the amount of uric acid in the daily urine was determined by the Hopkins-Folin-Shaffer method. Then purin bases were injected intravenously. This is held to be dangerous on account of embolism, but if 0.3 gm. of the substance is floated in 20 c.c. of water and dissolved in hot 0.1 n. sodium hydroxid and is given intravenously it is well borne; at most

there is fever up to 38.2° C. The uric acid and purin bases were estimated by the Krüger-Schmid method. The injected purin bodies were transformed into uric acid and excreted as such in varying amounts. But deficits of more than 60% were observed. Therefore it is still an open question whether there is catabolism of uric acid in man. Finally experiments were made with nucleosids, adenosin and guanosin. When adenosin was injected intravenously it appeared quantitatively in the urine in three days. There was no considerable increase in uric acid excretion after the injection of guanosin, which does not cause leukocytosis. Injected intramuscularly guanosin and adenosin caused considerable local reaction and in some cases fever. Nevertheless there was no considerable increase in uric acid excretion after adenosin. Guanosin was excreted in excess. On the whole it was found that injections of uric acid, purin bases and nucleosids in man do not result in a quantitative excretion of uric acid. There is a deficit, just as there is when these substances are given by mouth.

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**Resorption and Bacterial Decomposition of Purins in the Intestinal Canal of Man and Animals.**

*A. Schittenhelm and K. Harpuder, Ztschr. f. d. ges. exper. Med., 27:29, March 25, 1922.*

When nucleinic acid is administered to man only a part of it appears as uric acid in the urine. While Schittenhelm thinks there is an intermediate catabolism by way of uric acid, other authors believe that the purin bases undergo putrefaction in the intestine. Now Schittenhelm shows that only a small part of the purins undergo putrefaction, the existence of which is admitted. For the accurate determination of this factor 10 gm. Böhringer's yeast nucleinic acid was fed with 100 gm. barium sulphate and a dish of oatmeal gruel. Its passage into the large intestine was demonstrated roentgenologically. After six and eight hours the large intestine was emptied by means of an enema and the contents immediately analyzed. Uric acid and purin bases in the urine were determined by the Krüger-Schmid method, purin bases in the stools by the Krüger-Schittenhelm method. In 2 experiments, after the feeding of 10 gm. nucleinic acid, 22.2% and 16.1% of the purin bases reappeared in the urine. In the barium stool there was no increase in the purin base and in the second stool only a slight increase. The nucleinic acid was therefore certainly resorbed in the large intestine after it had been broken down there. Only a small part could have reached the large intestine and have undergone putrefaction there. Essentially the same results were obtained in an experiment on a dog with a fistula of the stomach and lower ileum. Only 4.68% of the purin bases fed in the form of thymonucleinic acid were discharged through the fistula. The allantoin of the urine was determined by Wiechowski's method.

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**The Fate of Repeated Injections of Uric Acid in Man.**

*A. Schittenhelm and K. Harpuder, Ztschr. f. d. ges. exper. Med., 27:34, Berlin, March 25, 1922.*

After experiments had shown that only a part of the ingested  
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uric acid or purin bases reappears in the urine, it remained to be determined whether the rest was retained, either in the blood or in the organs. Therefore organs, particularly the liver, spleen and kidneys of patients who had died of various diseases were analyzed nine to thirteen hours after death for their uric acid content. No uric acid was found in the spleen and kidneys, and the amount in the liver varied but was always very small. Then patients who were expected to die shortly were given daily injections of considerable amounts of uric acid (1-3 gm. in sodium hydroxid). At the same time the amount of uric acid in the daily urine was examined. The determination of the uric acid in the organs was made by Krüger-Schittenhelm's method, that in the blood by the method of Folin and Denis, but it was dealbuminized with 1.6% uranyl acetate and the result read in a graduated Autenrieth colorimeter. When the uric acid in the organs was added to that excreted in the urine there was still a considerable deficit as compared with the amount injected; a considerable amount had always disappeared. The greater part of the uric acid in the organs was found in the liver, which plays an important part in uric acid metabolism. The conditions are somewhat similar for the skin, bones and cartilages. In a case of contracted kidney an analysis of the blood showed that there was a considerable increase in its uric acid content, though this patient had only been given 4 gm. uric acid. Carcinoma patients who had been given 36 and 16 gm. uric acid showed only a slight increase in the uric acid content of the blood.

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**Studies in Creatin and Creatinin Metabolism. IV. On the Question of the Occurrence of Creatinin and Creatin in Blood.**

*Jeanette Allen Behre and Stanley R. Benedict. J. Biol. Chem., 52: 11, May, 1922.*

The available evidence that creatinin exists in blood may be thus briefly summarized: (1) Creatinin occurs in the urine, hence it is probably present in the blood. (2) The rate of color development in alkaline picrate solutions due to the blood component closely approximates that found for pure creatinin solutions. Neither of these arguments is conclusive, for the creatinin may be produced by the kidney, or the kidney may be able to concentrate this substance from dilutions in the blood very much greater than is commonly assumed. Furthermore, an unknown blood constituent might duplicate the rate of color production, and the possible presence of catalyzers affecting the reaction in blood filtrates must be considered. The authors believe that no results so far available offer definite evidence of the existence of creatinin in blood. In their study of the question they have applied certain reactions to both blood filtrates and pure creatinin solutions, and to creatinin added to blood, and have compared the relative behavior of true creatinin and of the blood creatinin, both before and after conversion of possible creatin into creatinin. Studies were made based upon the use of adsorptive reagents which would remove true creatinin from pure solution or from blood filtrates. In most of the creatinin determinations the authors employed the original picric acid method of Folin in which the blood is diluted to 5 times its volume with saturated picric acid, and the total solution saturated with picric acid. For

carrying out this saturation with dry picric acid, the mixtures were placed in a shaking machine for 5 to 10 minutes. By this technic not more than 4 or 5 mg. creatinin added to 100 c.c. blood could be recovered quantitatively. Doubling the volume of dilution permits the satisfactory recovery of the large quantities of creatinin. The authors also employed precipitation by means of heat coagulation, trichloroacetic acid, and tungstic acid, followed by saturation of the filtrate (after exact neutralization in the case of the trichloroacetic acid precipitation) with picric acid. Results by the various methods or precipitation indicated that for normal bloods the various precipitants yield parallel figures, while for bloods high in color-reacting substance the Folin-Wu precipitation with tungstic acid usually yields much higher figures than the picric acid precipitation. Heat coagulation filtrates showed still higher figures. The finding that creatinin does not exist in blood in detectable quantities does not necessarily minimize the value of the determination of the chromogenic substance for clinical or other purposes. In any method of creatinin determination in blood, except the procedure advocated by Folin and Wu, it is necessary to saturate a solution or mixture with solid picric acid. The Folin-Wu procedure yields colors too weak to be read accurately. For the precipitation, however, the Folin-Wu precipitation with tungstic acid is recommended, followed by saturation of a portion of the filtrate with dry picric acid in a shaking machine for about ten minutes.

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**The Utilization of Calcium and Phosphorus of Vegetables by Man.**

*N. R. Blatherwick and M. Louisa Long, J. Biol. Chem., 52:125, May, 1922.*

For a study of the availability of calcium and phosphorus in vegetables for man 2 healthy young women volunteered as subjects at the same time continuing their regular occupations. The diet in the first period of 4 days was planned to approximate as closely as possible the maintenance requirements for calcium, phosphorus, and nitrogen as given by Sherman. For the second period of 7 days the diet of subject "O" was altered by the substitution of 0.5 gm. phosphorus with an equivalent amount of phosphorus from vegetables. The diet of subject "L" in the second period differed from that of the first by the addition of 0.5 gm. of vegetable phosphorus. The vegetables eaten included lettuce, asparagus, celery, spinach, summer squash and cabbage. Distilled water only was used in cooking the vegetables and for drinking purposes. Chemically pure sodium chlorid was also used throughout. The authors have tabulated (1) the kinds and amounts of foods eaten, with daily intake of calories, protein, calcium and phosphorus, (2) the daily output of calcium, phosphorus, and nitrogen in the urine of each subject, and (3) the intake, output, and balance of calcium, phosphorus and nitrogen. The data presented indicate that calcium and phosphorus derived from vegetables are capable of meeting the maintenance needs of man.

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**The Mineral Metabolism of the Milch Cow.**

*E. B. Forbes, J. A. Schulz, C. H. Hunt, A. R. Winter and R. F. Remler, J. Biol. Chem., 52:281, May, 1922.*

The authors have attempted to study the course of the mineral metabolism of the milch cow throughout the whole of the annual cycle of lactation and gestation. As in their previous observations, their method involved the complete chemical accounting for feed, milk, urine and feces. Six mature Holstein-Friesian cows were used, in three series of balance determinations, the collection periods being either sixteen or twenty days in length, and normally separated by ten-day intervals during which the subjects received the same ration which was to be used in the collection period to follow. The cows were entirely dry in 7 balance determinations, and in 4 more were giving less than 10 lbs. of milk a day. In the remaining 7 balance determinations the cows yielded from 37.87 to 61.36 lbs. of milk a day. The balance periods covered, with some interruptions, the entire cycle, from the first day of lactation to the day before parturition. Tables show the stage of lactation and gestation covered by the experiment; enumerate the individual balance periods, with designation of stages of lactation and gestation to correspond, arranged in natural sequence; record the average daily feeds consumed, milk produced, and gain or loss in live weight; the chemical composition of the milk; the average daily balances of minerals and of nitrogen, in the different periods and with the varied rations. The results indicate that the calcium metabolism of the milch cow, while fed on winter feeds, is characterized by rapid loss from the body during the early part of the lactation period, changing to retention late in the period of lactation; by continued retention during the dry period, with most rapid storage at the end of the period of gestation. The principal factors determining the loss of calcium during the early part of the lactation period are the impulse to secrete, as accentuated by selective breeding, and a limited ability to assimilate calcium. The dry cow, on dry feeds, can store calcium at a rate at least equal to that at which the fresh cow, on dry feeds, loses calcium. The calcium of the bones was found to be more readily available, for purposes of milk elaboration, than the calcium of the ration and of mineral supplements. A marked but not complete interdependence of calcium and phosphorus in metabolism was manifest. Phosphorus may be stored during liberal milk production; calcium never seems to be stored under these conditions, at least on winter rations. The proportionate elimination of minerals by urine and feces bore no definite relation to mineral balances. Many negative mineral balances were determined which could not signify insufficient intake. This investigation suggests to the authors the desirability of building up extensive mineral reserves in growing heifers by liberal allowance of feeds rich in mineral nutrients, and also the importance of a dry, resting period of adequate length to permit the restoration of all previous nutrient overdrafts, with liberal feeding during this period.



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**Amino-Acids in Nutrition. V. Nutritive Value of Edestin (Globulin from Hemp Seed), Cystin and Lysin as Growth-Limiting Factors in That Protein.**

*Barnett Sure, Am. J. Physiol., 61:1, June 1, 1922.*

The rations fed the rats in this investigation were as strictly synthetic as it was possible to make them. The proteins used were the only source of nitrogen with the exception of the small amounts introduced by the alcoholic extracts of the wheat embryo to furnish water-soluble vitamin B. The amounts of foreign nitrogen thereby introduced constituted only 2% of the total protein. The growth curves of the animals show that edestin when fed as 12 and 18% of a ration, carrying 2% of the total protein in the form of nitrogen of unknown source in alcoholic extract of wheat embryo to furnish water-soluble vitamin B, is inadequate for growth. Growth responses to cystin were obtained, but only in the presence of lysin. Similarly when cystin was administered in the edestin rations in the presence of gelatin, having a high lysin content, the growth was increased 31.4%. The author concluded that cystin and lysin at least are two amino-acids responsible for the deficient quality of edestin.

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**A Note on the Nutritional Adequacy of the Proteins of the Chinese and Georgia Velvet Beans with Reference to Amino-Acid Composition.**

*D. Breese Jones, A. J. Finks and H. C. Waterman, J. Biol. Chem., 52:209, May, 1922.*

Recently Barnett Sure presented the results of experiments which he interprets as indicating that the proteins of the Georgia velvet bean are inadequate because of amino-acid deficiency and states that "cystin is unquestionably a growth-limiting factor in the proteins of the Georgia velvet bean." Sure refers to the publication of Waterman and Jones on the digestibility in vitro of the proteins of the Chinese and Georgia velvet beans, and states that these authors conclude that amino-acid deficiency cannot account for the failure of the velvet bean proteins to promote growth. Sure conveys the impression that the statement of Waterman and Jones which he cites was based solely on the results of chemical analyses of the velvet bean proteins, and on the results obtained by the digestion experiments in vitro, since he makes no reference to the publication of Finks and Johns giving the results of their feedings experiments. Sure has also apparently overlooked the authors' further statement immediately following the passage which he cites, i. e. that the proteins from either the Georgia or the Chinese velvet beans gave normal growth when prepared by coagulation. Jones and Finks wish to correct the impression conveyed by Sure and to make it clear that their statement referring to the amino-acid adequacy of the velvet bean proteins was based primarily on the fact that growth at the normal rate was obtained when the total proteins prepared by coagulation were fed to albino rats as the sole source of protein in a diet otherwise adequate. That normal growth was obtained

on the isolated velvet bean proteins after the indigestibility factor had been eliminated by heating proves that the amino-acids essential for growth are present in these proteins in adequate amounts.

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**A Study of the Metabolism and Respiratory Exchange in Poultry During Vitamin Starvation and Polyneuritis.**

*R. J. Anderson and W. L. Kulp, J. Biol. Chem., 52: 69, May, 1922.*

The following investigation was undertaken to obtain information regarding changes that may occur in the metabolism or variations in the respiratory exchange of poultry during vitamin starvation, the latter condition being produced in chickens by feeding them with polished rice. In studying the respiratory exchange a small respiration apparatus was used, a duplicate of the one described by Murlin. The plan of the experiments embraced a study of the normal basal metabolism; the metabolism during digestion of grain and mash, and of rice; during vitamin starvation and during polyneuritis; after recovery from polyneuritis; effect of vitamin starvation and polyneuritis; respiratory exchange of chickens under normal conditions in comparison with vitamin starvation and polyneuritis; calculation of the nonprotein respiratory quotient and heat production; metabolism per kilo per hour; percentage loss in weight and decline in heat production; protein metabolism on an exclusive rice diet; potassium and phosphorus metabolism on an exclusive rice diet; and metabolism after recovery from polyneuritis. The first apparent effect on poultry of a diet of polished rice was a loss of appetite which continued until food was refused entirely. A gradual but continuous loss in weight occurred accompanied by a decline in heat production. There was no noticeable change in the respiratory quotient during vitamin starvation. In this period the most striking effect was the inability of the animals to utilize a normal quantity of food and the consequent decided decline in heat production. The metabolism dropped to a very low point when polyneuritis had progressed so far that symptoms of paralysis appeared. The respiratory quotient seldom rose above 0.75 during this stage of polyneuritis, although the crop contained much undigested rice, indicating an almost complete inability at that time to utilize this food. After the animals recovered from polyneuritis the metabolism and the heat production rose rapidly, but the appetite remained poor and the gain in weight was very slow.

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**Qualitative Undernutrition. I. Rat Beriberi.**

*Franz Hofmeister, Biochem. Ztschr., 128: 540, Berlin, March 28, 1922.*

Attempts were made to prepare the accessory food known as vitamin B, whose lack induces the insufficiency disease termed beriberi. The experiments were conducted on rats, and data regarding the attacking point of vitamin B deficiency were collected. The experimental procedure was so conducted as to preclude the beriberi animals from consuming their own feces, as coprophagy is antagonistic to vitamin

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deficiency. The animals were fed on casein, starch, cod-liver oil, fat and the requisite inorganic nutrient salts. The fat accordingly contained only fat-soluble vitamin A. A slight addition of material containing vitamin B (yeast, yeast extract, carrot juice) manifests itself immediately by retardation of insufficiency symptoms. In rats the disease-picture showed a distinct incubation period, a stage characterized by ataxy of spontaneous movement, a stage of spastic phenomena and forced movements, and finally a stage of increasing central paralysis leading to death. The indecision and deficient will-power exhibited by the animals is remarkable. Nerves and brain were subjected to anatomic investigation. A comparison of the disease symptoms and anatomic phenomena shows that in rat beriberi there may be no anatomically recognizable degeneration of the peripheral nerves even in the most pronounced cases. It is therefore not correct to designate the condition as polyneuritis. On the other hand, changes in the central nervous system occur in all severe cases, particularly multiple hemorrhages in the cerebellum and brain-stem, as well as degeneration of nervous elements. The extension and number of the hemorrhages proceeds unmistakably parallel to the intensity of vital nervous disorders, ataxy, spasms and forced movements. The pathologic-anatomic diagnosis should accordingly be, not polyneuritis, but multiple cerebral hemorrhages (cerebral purpura) and is to be classed with the pictures of so-called hemorrhagic encephalitis, such as are observed in chronic alcoholic, arsenic and lead poisoning. Regarding the genesis of the disease-picture the following conception is put forward. The functioning elements of the nervous system, the ganglion-cells, their processes and axis-cylinders, require an adequate supply of vitamin B. Under a permanent deficiency of this their functions cease and they finally degenerate. These changes proceed at different rates in the different nerve regions and the animal species has a decisive influence on them. In man and in fowls the peripheral nerves seem to be affected first and more severely, while in rats and pigeons the central nervous system is the first to suffer. The analogy to the nervous sequels of chronic alcoholic, arsenic, and lead poisoning disclosed by these researches is accordingly to be regarded as a confirmation of the intoxication theory. In a practical sense the course of the rat disease indicates that the prospects of a cure by means of the administration of antineuritic preparations apply only to that stage in which no irreparable changes, such as considerable hemorrhages or extensive degenerations, have as yet made their appearance. Thus, the way is shown to the application of curative measures.

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#### **Occurrence of Anemia in Rats upon an Insufficient Diet.**

*William M. Happ, Bull. Johns Hopkins Hosp., 33: 163, May, 1922.*

The well-known frequency of anemia in children with rickets led Happ to undertake extensive studies upon the blood-picture in rats made rachitic by faulty experimental diets, and in rats given other defective diets which do not produce rickets. The animals were fed upon formulas provided by E. V. McCollum, and were kept under carefully controlled conditions. Blood was obtained from a large



superficial vein, and counts of the cells, hemoglobin estimations, and stained smears were made by constant technic. Normal figures were established for young rats, which were found to have fewer red blood-cells and leukocytes, and less hemoglobin than adult rats, but higher lymphocytic proportion. Diets low in iron, but otherwise well-balanced, do not produce anemia in the first generation, nor do diets consisting solely of milk or bread and milk. In the second generation, however, rats may show slight anemia on these diets. Diets deficient in the fat-soluble vitamin A or water-soluble vitamin B, do not produce anemia in the rat. If water-soluble B is so low as to produce polyneuritis, a severe leukopenia results. Diets low in an unnamed organic substance which occurs in cod-liver oil, with low calcium but high phosphorus content, cause rickets-like changes associated with anemia, often also with enlargement of the spleen, the whole picture resembling the anemias seen in association with rickets in human beings (von Jaksch's anemia). A diet low in the organic substance of cod-liver oil and low in phosphorus with normal calcium content, which produces severe rickets, does not cause anemia.

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**The Antiscorbutic Vitamin. I. A Study of Its Solubility from Desiccated Orange Juice.**

*E. B. Hart, H. Steenbock and S. Lepkovsky, J. Biol. Chem., 52:241, May, 1922.*

The authors present data on the solubility of this vitamin in various organic solvents, including butyl alcohol, methyl alcohol, various concentrations of ethyl alcohol, chloroform, ether, ethyl acetate, acetone, petroleum ether, and benzene. Guinea-pigs were used as test animals and were fed a scorbutic ration containing the extracts of orange juice. Presence or failure of growth of the animals was the criterion of solubility of the vitamin in the solvent. The authors found the antiscorbutic vitamin of desiccated orange juice to be soluble in 80%, 95%, and absolute alcohol (ethyl). It is also soluble in methyl alcohol. This vitamin of desiccated orange juice was found to be insoluble in butyl alcohol as well as in benzene, petroleum ether, acetone, ether, chloroform, and ethyl acetate. The behavior of this vitamin toward organic solvents and water indicates that it is not of fat or lipin character.

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**The Partial Pressure of Oxygen in the Blood During Progressively Induced Anoxemia.**

*Charles W. Greene and Carl H. Greene, J. Biol. Chem., 52:137, May, 1922.*

Two series of experiments were carried out in a study of this problem. Dogs were operated on under chloretone analgesia that did not suppress or weaken either respiratory or vascular reflexes. A "rebreather" apparatus was connected by a short tracheal tube and the animal was allowed progressively to exhaust the oxygen from the air enclosed in the system. The carbon dioxide was absorbed by potassium

hydroxid and completely removed from the inhalant air. Graphic records of the blood pressure and the respiration were taken as the animal progressively exhausted the oxygen from the air enclosed in the apparatus and samples of air and arterial and venous blood drawn simultaneously at intervals during the course of the experiments. The blood samples were analyzed for their oxygen content and the air for oxygen and carbon dioxid. In the first series of experiments the oxygen content of the inhalant air was, of course, found to be greater than that of a corresponding sample of alveolar air. In the second and more extensive series of experiments, alveolar air was drawn through a small sound inserted deep in the bronchial tree, just short of occluding the terminal bronchus. This method gives a mixed sample of alveolar air closely approaching the average composition of the air in contact with the pulmonary epithelium. The air samples were analyzed by the Haldane method, and the blood by a modification of the Van Slyke method. In a few tests arterial blood samples were also equilibrated against the alveolar air.

Tabulated data show that lowering of the percentage saturation of the arterial blood in dogs breathing air progressively reduced in oxygen tension closely parallels the dissociation curve determined in vitro by Barcroft and Camis. The proponents of the secretory theory have assumed that the capacity for oxygen secretion exists but is called forth only during extreme oxygen lack. Although the conditions of the authors' experiments were probably adequate to call forth this mechanism, if present, no evidence of its presence was discovered. Neither was any evidence obtained of an arterial oxygen tension higher than that in the alveolar air. When alveolar air was exposed to a simultaneous sample of arterial blood, oxygen was absorbed by the blood. Section of the vagi was without effect on the degree of saturation of the arterial blood during progressive anoxemia. By these investigations the current conception of a purely physical mechanism regulating the passage of oxygen through the pulmonary epithelium is confirmed for all stages of anoxemia.

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**The Exhalation of Carbonic Acid by Air-Breathing Aquatic Insects.**

*W. v. Buddenbrock and G. v. Rohr, Pflüger's Arch. f. d. ges. Physiol., 194: 218, Berlin, March 24, 1922.*

Krogh thought that the greater part of the carbonic acid exhaled from the insect's body is not exhaled through the trachea but through the skin. The authors showed that this theory did not hold good for the grasshopper. They also repeated Krogh's experiments on the larvas of the water beetle (*Dysticus marginalis*), and determined the respiratory quotient directly by means of Krogh's respiratory manometer. They found, as in the grasshopper, that the carbonic acid excreted through the skin was less than 25% of the total amount of carbonic acid. Therefore Krogh's theory, which was also accepted by Franckenberg, is not true of the larvas of the water beetle. Similar results were obtained with larvas of *Eristalis*.

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**Obtaining the Alveolar Air and the Size of the Noxious Space in Dogs.**

*Fr. W. Krzywanek and Maria Steuber, Pflüger's Arch. f. d. ges. Physiol., 194:477, Berlin, April 20, 1922.*

In a well-trained dog the fasting value by the Zuntz-Geppert method and by taking the air from the piece connecting the crossing of the respiratory valve and the lung, or from the latter itself, was determined at about 35.5 mm. Hg. for alveolar CO<sub>2</sub> tension and 31.3 c.c. for the noxious space. Subsequent experiments will compare these data with those found in men and will determine the use of the method in the latter.

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**The Dependence of the Force of Respiration on the Condition of Expansion of the Respiratory Organs. Remarks on the Work of Senner on "Respiration in Moving Air."**

*Fritz Rohrer, Pflüger's Arch. f. d. ges. Physiol., 194:149, Berlin, March 24, 1922.*

The values found by Senner for the passive force of respiration agree quite well with those of Rohrer and those of Bernouilli, as does also the nature of the curve of maximum inspiratory and expiratory respiratory pressure. But Senner's values for maximum pressure are considerably lower, as he found a maximum expiratory pressure of +82 cm. water after extreme inspiration and a maximum inspiratory pressure of —103 on extreme expiration, while Rohrer found values of +142 and —138 cm. Senner's values can only have an individual significance, as the maximum expiratory pressure in man is always over 100 mm. mercury, and therefore over 136 cm. water. Rohrer agrees with Senner's assertion that on respiration in moving air the balance of the respiratory organs is displaced in the inspiratory direction.

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**The Effect of Temperature on Gaseous Metabolism in Insects.**

*W. v. Buddenbrock and G. v. Rohr, Pflüger's Arch. f. d. ges. Physiol., 194:468, Berlin, April 20, 1922.*

The author found in *Dixippus* that the oxygen intake between 12° and 32° C. is in simple proportion to the temperature, that is, that the curve runs in a straight line, while below 12° C. higher oxygen values are found than would correspond to the curve elsewhere. This striking finding is not in accordance with experiments on the metabolism of cold-blooded animals. Therefore experiments were made on other animals, especially on motionless insects, for which the pupas of *Calliphora* and of butterflies were used, as well as the caterpillar stage of butterflies. The metabolism curve during complete rest is a straight line. The variations in the curve in the desquamating caterpillar is probably due to the active processes of secretion which take place at this time. It is to be assumed that other variations in the linear curve of resting metabolism is due to superposition of other factors.

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**Comparative Study of the Reciprocal Innervation of Muscles with One and Two Articulations.**

*I. S. Beritoff, Pflüger's Arch. f. d. ges. Physiol., 194: 365, Berlin, April 20, 1922.*

The experiments were made on decerebrate cats; the muscles of the hind legs were isolated by Sherrington's method. The experiments involved the reciprocal innervation of the individual heads of the quadriceps femoris, that of the double articulated head (caput longum) and of the single articulated one (caput mediale and lateralis) of the triceps brachialis, as well as the mono-articulated flexor of the elbow joint, the brachialis, and the diarticulated biceps. The diarticulated muscles all showed the same fundamental characteristic; they contract on movements of flexion and extension of the whole extremity depending on the anatomic position of their distal end. If the muscle, as a result of this position, cause an extension of the distal limb, as is the case for example in the rectus femoris, it contracts unconditionally on all movements of extension of the extremity and is inhibited on movements of flexion. But if the muscle brings about a movement, as for example in the biceps brachii, it contracts on all general movements of flexion of the extremity and is inhibited on all movements of extension. An opposite anatomic position of the proximal end of the muscle does not hinder the performance of the above-named movements, it even supplements them, as the mechanical, together with the general, stretching, strengthens the activity of the distal end. The innervation of the diarticulated leading muscle parallels that of its mono-articulated partner which acts on the same joint.

These same laws for the action of the diarticulated muscles is true also for the corresponding muscles of the frog. In this animal the triceps femoris and gastrocnemius which bring about an extension of the distal and a flexion of the proximal joint, take the chief part in a general movement of extension of the extremity, while the semitendinosus and tibialis which cause a flexion of the distal and an extension of the proximal joint are unconditionally involved in the general flexion of the extremity. For the functional significance of the diarticulated muscle, that is, for the character of reciprocal innervation with uniform movement of all the joints of a limb therefore, the anatomic relationship to the distal joint is decisive. If it extends the joint, then, on extension, stimulating innervation impulses are sent to it and inhibiting innervation on flexion; if it flexes the distal joint this state of affairs is reversed.

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**Synergic and Reciprocal Innervation of Antagonistic Muscles from Experiments on Man with Observations on Their Reaction Time.**

*Albrecht Bethe and Hermann Kast, Pflüger's Arch. f. d. ges. Physiol., 194: 77, Berlin, March 24, 1922.*

The separation of muscles from the joint mechanism in human beings operated upon by Sauerbruch's method makes an accurate study of the mutual relations of these muscles possible, just as in Sherring-

ton's experiments on animals. These muscles are to be regarded as normal with reference to nutrition and innervation, and are merely decreased considerably in strength. Reflexes cannot always be preserved by the canalized muscles for as a result of the operation the reflexogenic zones, the tendons, periosteum and skin, are removed.

These experiments dealt with voluntary movements of the antagonists, 12 combinations of which are theoretically possible; all these play a part in patients who have had amputations, and many also in the intact limb. The movements are divided into: I. Syndromes; and II. Antidromes. In the former the movement in the 2 antagonistic muscles is in the same direction, either contraction or relaxation. In the latter the movement in one muscle is opposite to that in the other. Both groups are subdivided into positive and negative movements; positive when both muscles or the dependent muscle group cause contraction, negative when the reaction causes relaxation. That muscle is called dependent whose movement is not voluntary but evidently accompanies the movement of the voluntarily moved muscle. The following combinations of movement exist: I. Syndromes: (1) Positive: (a) simultaneous double contraction; and (b) involuntary rise of tonus of the resting dependent muscle; (2) Negative: (a) relaxation of both muscles; (b) involuntary initial decrease of tonus of the resting dependent muscle; and (c) involuntary interim decrease of tonus of the already voluntarily contracted dependent muscle. II. Antidromes: (1) Positive; (a) involuntary relaxation of one with voluntary contraction of the other muscle group (Sherrington's reciprocal inhibition); (b) involuntary rise of tonus of the resting dependent muscle with relaxation of a muscle group; and (c) involuntary rise of tonus of the already contracted muscle with relaxation of another muscle group; (2) Negative; (a) identical with II. 1 a; (b) involuntary initial decrease of tonus of the resting dependent muscle with voluntary contraction of the antagonist; and (c) involuntary interim decrease of tonus of the contracted muscle during contraction of the antagonist.

Of all these combinations of movement Sherrington's reciprocal inhibition is the most frequent; it appears both in the resting muscle in a condition of tonus and in the contracted muscle. Occasionally however there is a rise of tonus in the resting muscle when its antagonist contracts. When both muscles are contracted a relaxation of the one, in man as well as in animal experiments, may bring about a contraction of the other; but a temporary partial relaxation may also occur. If a muscle is in a state of continuous contraction generally, as in animal experiments, a contraction of its antagonist usually produces an inhibition, but sometimes an increase, of the contraction. The recoil phenomenon, the successive induction of Sherrington, to which Isselin attributed great importance in the normal sequence of movements, was generally entirely absent or was only observed occasionally on rapid movement. If a muscle relaxes, its resting antagonist either shows a decrease of tonus or a slight steady rise in tonus, but no true contraction. In the relaxing muscle itself there is usually no recoil movement. The reaction time of the canalized muscle groups to electrical and optical stimuli shows hardly any variation from that of the same muscles in the normal arm.



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**Latent Periods in the Reciprocal Action of Antagonistic Muscles.**

*J. M. D. Olmsted and W. P. Warner, Am. J. Physiol., 61:106, June 1, 1922.*

Upon repeating certain of Sherrington's experiments on reciprocal innervation the authors were convinced that antagonistic muscles do not act exactly simultaneously, but that the contracting muscle begins its action earlier than its relaxing antagonist. The experiments were performed on cats decerebrated by the Sherrington decerebrator. The antagonistic muscles used were the vastus internus (extensor) and semitendinosus (flexor). The former was left in place, and a lever, attached to the stump of the lower limb, which had been amputated below the knee, recorded the movements of this extensor muscle. The semitendinosus was cut away from its insertion into the tibia and the freed tendon was connected to a lever. The muscle was then entirely loosened from all attachments up to a short distance above the knee. All nerves in the region were cut except those supplying the muscles studied. Both ipsilateral and contralateral stimuli were employed. The afferent nerve in each case was the sciatic and the source of current an interrupted one from the secondary coil of an inductorium. Records were taken on a smoked drum moving at the rate of 27.5 cm. per second. It was found that in the reciprocal action of antagonistic muscles as studied in the flexion and crossed extension reflexes, contraction occurs slightly before relaxation. This relationship also held when one reflex was replaced by the other, in the so-called dilemma of reaction, and in rhythmic movements during stimulation. The reverse is true in the phenomena of rebound. The results are in accord with the motor center theory which assigns to a collateral branch between the motor centers the function of inhibition.

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**Muscle Fatigue and Its Relation to Muscle Innervation.**

*Leon Asher, Pflüger's Arch. f. d. ges. Physiol., 194:230, Berlin, March 24, 1922.*

Experiments on stimulation of muscle-nerves of uninjured rabbits with continuous registration (generally with the use of tetanizing stimuli with a frequency of 50 per minute) showed only a partial exhaustion with isotonic contractions, even with tetanizing stimuli, that acted every 2 seconds. The decrease of contraction height that took place after some time (beginning fatigue) reached 40 to 50% of the beginning height and sometimes lasted for hours with continuous stimulation. This relative indefatigability is still greater with isometric contractions. According to this, under conditions as nearly physiologic as possible, the muscle as well as the motor nerve are to a great degree inexhaustible. Fatigue therefore is caused centrally to a much greater extent than has heretofore been believed. Extirpation of the sympathetic on one side does not cause any difference as compared with the other side of the body. In frogs tetanizing stimuli cause rapid exhaustion. With an induced current giving stimuli every 4 seconds there is practically no

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fatigue; but with stimuli every 4 seconds there is fatigue after about  $\frac{1}{2}$  hour. This is therefore the critical interval in which the balance between the phases of dissimulation and assimilation is disturbed. When the posterior root is cut on one side, fatigue takes place on the injured side considerably later than on the other. Injection of atropin and novocain locally into the muscle has no effect, but acetyl cholin, like cutting the posterior root, causes a delay in fatigue. If it is assumed that the acetyl cholin stimulates the parasympathetic mechanism of striated muscle, the severer fatigue is an expression of the increased stimulation of the parasympathetic nerves.

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**The Relation between the Induction Opening and Closing Contractions in Muscles Stimulated Directly or Injured by Narcotics or Trauma.**

*Marta Faenkel, Pflüger's Arch. f. d. ges. Physiol., 194:20, Berlin, March 24, 1922.*

If a normal muscle in Ringer's solution is stimulated by an induced current, the conditions are the same as those in muscle in the air, that is the closing contraction is smaller than the opening contraction so long as the current is not maximal. In this case opening and closing contractions are almost equal. If the strength of the current is decreased the closing contraction rapidly becomes smaller and disappears at a time when the opening contraction is still considerable. Incomplete narcosis and acute narcosis with certain substances do not cause any change in these relations. But most narcotics in rapid total narcosis cause the opening and closing contractions to decrease to the same degree so that quite small opening contractions are still accompanied by considerable closing contractions.

The material for experimentation was the sartorius muscle of *Rana temporaria*, *R. esculenta* and *Bufo vulgaris*. The narcotics examined were methyl, ethyl, propyl, amyl and heptyl alcohol, ethyl and phenyl urethan, benzamid and salicylamid, cane sugar and potassium chlorid. The narcotic action of the last 2 substances is due to colloidochemic changes. Many of these substances, for example propyl alcohol, cause a beginning increase in the size of the opening and closing contractions; in this case even before narcosis is complete the closing contraction may have disappeared while the opening contraction still persists. The conditions in incomplete narcosis are analogous to those with increased calcium content and are due to the increased sensitiveness of the muscle to the steepness of the current with low concentrations of the narcotic. In rapid narcosis the heights of the contractions decrease about proportionally; this may be due to the fact that the stimulus and the chemical process resulting from it are essentially unchanged, while the action of the shortening substance on the contractile parts of the muscle is inhibited. Certain differences in the use of the ascending and descending direction of the induced current depend on the nature of the narcotic. Generally with descending currents the closing contraction becomes ineffective soonest; with ascending currents, the opening contraction. An apparent reversal was found in mechanical injuries of muscle, and the contractions produced became lower. Thermic injuries caused a true reversal. The height of the contractions do not

give any definite information as to the greater excitability of the end of the muscle. When the whole muscle was immersed in Ringer's solution, the contractions were higher with the ascending or the descending current, depending on the strength of the current.

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**The Chemical Contraction of the Mammalian Muscles When Electric Irritability Is Preserved or Abolished.**

*Adolf Schott, Pflüger's Arch. f. d. ges. Physiol.*, 194: 271, Berlin, March 31, 1922.

The contraction of muscle as a result of the action of chemicals is regarded either as a result of irritation, that is as tetanus, or as a manifestation of an action on the contractile substance. Bethe, Fraenkel and Wiemers have attempted experimentally to prove this for muscles of cold-blooded animals. In continuation of these experiments, surviving muscles of mammals were made incapable of electric stimulation by cooling, heating almost to the point of rigidity, or by prolonged immersion in Ringer's solution, after which they were tested with substances that produce contractions, with reference to differences as compared with electrically irritable muscles. For the experiments the isolated rectus abdominis muscles of white mice were kept in oxygen-free Ringer's solution. These were stimulated with the induction current. The temperature varied from 1° to 60° C. The stimulating substances were chloroform (saturated in Ringer's solution with sodium bicarbonate), 0.02 n. sodium hydroxid and 0.1 n. hydrochloric acid. The contracting action of chloroform, sodium hydroxid and hydrochloric acid is not dependent on electric irritability of the muscle. To be sure contraction caused by hydrochloric acid is dependent to a great degree on the condition of the muscle but not on its electric irritability, as hydrochloric acid may not produce any contraction when kinogeny (electric irritability) is preserved, and on the other hand it may cause contraction when kinogeny is abolished or greatly decreased. While chloroform and sodium hydroxid are effective at all temperatures, hydrochloric acid is ineffective at 1°-5° C. If sodium hydroxid is allowed to act after chloroform, contraction is generally stopped, but a cumulative contraction may appear. Hydrochloric acid after chloroform always cancels the contraction; chloroform after sodium hydroxid may either be ineffective or stimulate contraction. But no parallelism has been found in the muscles of warm-blooded animals between kinogeny to induction currents and chemical contraction. The fact that muscles at low temperatures or after lying for a long time cannot be caused to contract by hydrochloric acid, but can by chloroform or sodium hydroxid, indicates that in contraction a preponderant rôle is played by acids (lactic acid). The abolition of the chloroform contraction by hydrochloric acid indicates the same thing.

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**The Chemical Contraction of Narcotized Muscle as Compared with Normal Muscle.**

*Albrecht Bethe, Marta Fraenkel and Josef Wilmers, Pflüger's Arch. f. d. ges. Physiol.*, 194: 45, Berlin, March 24, 1922.

It is probable that a true contracting substance does not act by  
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way of a chemical stimulation but directly on the contractile molecules of the muscle. The possibility of the penetration of such substances is admitted for the lipoid-soluble substances, such as chloroform and alcohol; it is very probable for acids and bases and has been definitely proved for potassium salts. The experiments were made on the sartorius muscle of *Rana temporaria* with the same methods as those used by M. Fraenkel. The typical contracture-producing substances used were sodium oxalate in isotonic solution, which produces fibrillary twitchings and tetanoid continued contractions; chloroform as a representative of organic substances with high surface activity, in saturated solution (Ringer) or diluted 1:1, or 2:1; 0.005 N or 0.01 N hydrochloric acid in Ringer's solution; and 0.02 sodium hydroxid in Ringer's solution and ammonia. If the sartorius is narcotized with medinal, salicylamid, urethan, methyl, propyl or amyl alcohol or calcium chlorid until there is no mechanical response to stimulation with the induced current, a strong contracture can still be produced by chloroform, hydrochloric acid and sodium hydroxid. This contracture, if the contracture substance has not acted too long, can be broken off by Ringer's solution. The nature of the narcotic used has no effect on the chloroform contracture. The latent period is shorter than in control muscles and the rise in the curve steeper. But some narcotics have a depressant action on hydrochloric acid and sodium hydroxid contracture, with some narcotics in hydrochloric acid contracture, as well as in chloroform, there is a steeper rise of the curve and often an increase in the height of the maximum contracture but a shortening of the time it remains at the maximum.

Depressive narcotics, for example heptyl and methyl alcohol, decrease the steepness and the contracture height and shorten the maximum time. The steepness is unchanged in sodium hydroxid contracture, the contracture height somewhat decreased, and the maximum time somewhat shortened; with depressive narcotics, methyl and heptyl alcohol, cane sugar and medinal, the steepness and contracture height decrease, the maximum time increases. The sodium hydroxid contracture can be completely suppressed with cane sugar and medinal, but this is not true of the hydrochloric acid contracture. Therefore the chemical contracture of the muscle is independent of the mechanical sensitiveness of the muscle to mechanical stimuli. The electrical stimulus brings about in the muscle: (1) the appearance of differences of electrical potential and therefore the giving off of electrical energy; (2) chemical transformations; (3) increase of heat, and (4) mechanical effects such as contraction, tetany and increase of tonus. The electrogonia (1) is in part a direct expression of the changes in concentration caused by the stimulus. The chemogonia (2) is a result of this change of concentration and probably manifests itself also in the electrical phenomena. The thermogonia (3) on the other hand is dependent largely on the chemical, to a lesser degree on the mechanical, processes. The only process that can change independently is the terminal process with kinogonia (4). In narcosis, stimuli act electrically and thermally but kinogonia is suspended. As the chemical contracture, even with a fourfold dose of the narcotic may attain the same height and steepness as in normal muscle, it is impossible to attribute its origin to a process of stimulation. Therefore the contracture substance must act immediately on the contractile

molecules. The depressive action of many narcotics is due to the fact that they keep the contracture substance away from the contractile molecules.

The experiments also make it seem probable that the physiologic contracture substance does not originate in the contractile molecules themselves, but outside them. While these experiments do not actually prove the immediate action of the contracture substance on the contractile molecules yet they very greatly increase the probability of the theory.

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**The Effect of Nonstimulating Continuous Perfusion on the Permeability of Frogs' Muscle.**

*Herrmann Weiss, Pflüger's Arch. f. d. ges. Physiol., 194:152, Berlin, March 24, 1922.*

In muscle activity, according to Embden, there is a marked increase in the discharge of phosphoric acid from the muscle. There is an increased permeability of the boundary layers of the muscle-fiber, which plays an important part in fatigue, just as the loss of excitability of a muscle kept in isotonic cane-sugar solution is due to the development of an abnormal permeability of the membrane-like boundary layer of the muscle-fiber; also the gradual decrease in stimulability of a frog's muscle kept in oxygen-containing Ringer's solution is due to an increased permeability manifested by the excretion of phosphoric acid. The increased excretion of phosphoric acid is accompanied by an increased penetration into the muscle of potassium ions. Up to a certain degree the muscle stimulability in all these cases is better the less the permeability of the boundary layer. Experiments should now be made with a view to determining whether electric currents that do not cause any contractions have an effect on permeability. The effect of the constant current was tested on the gastrocnemius, semimembranosus and sartorius muscles of *Rana esculenta*, which were kept continuously in fluid into which a sufficient amount of oxygen was introduced. The permeability of the muscle-fiber boundary layer increased, as was manifested by a decrease of stimulability, an increased excretion of phosphoric acid, and a more rapid development of potassium paralysis. It has not yet been shown whether there was also increased excretion of lactic acid. It is possible that a change in the concentration of the neutral salts of the plasma membrane or a displacement of the pH at the limiting membrane is the cause of the reversible injury of the membrane.

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**The Relations of the Vegetative Nervous System to the Tonus of the Skeletal Muscles.**

*Erich Deicke, Pflüger's Arch. f. d. ges. Physiol., 194:473, Berlin, April 20, 1922.*

Experiments were made to test whether stimuli applied to the sympathetic and to the posterior roots would have a motor effect on the striated muscles. The rami communicantes of the marginal column of the sympathetic were stimulated electrically for this purpose with an induction current, the posterior roots were stimulated electrically and

mechanically (section and crushing). Possible motor effects on the skeletal musculature were controlled by the observation of changes in form and action currents. Frogs were used as experimental animals. In none of the experiments was any action observed on the striated musculature, indicating that the sympathetic and posterior roots have no effect on the tonus of the skeletal muscles.

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**A Study of Sensibility of the Viscera.**

*W. R. Hess and W. H. v. Wyss, Pflüger's Arch. f. d. ges. Physiol., 194: 195, Berlin, March 24, 1922.*

Experiments were made to determine whether, aside from the sensation that can be produced from the mucosa, there are other sensory receptors in the viscera. As indicators of a sensory reaction, based on experience with Goltz's percussion experiment, the effect on heart action was chosen, and the reactions of the skeletal muscles were also observed. The mechanical stimuli used were pinching, touching with a hair, traction, insufflation of air and distension; for chemical stimulation sponging with sponges dipped in acetic acid; for thermal stimulation hot or cold metal rods, and an induced electric current. The experiments were made on decerebrate frogs. Touching the stomach caused an isolated inhibition of the action of the auricle of the heart; on stronger mechanical stimulation the inhibition extended to the ventricle, so that only the sinus kept up its rhythmic activity. In mechanical stimulation the reaction of the heart is greatest, while in chemical stimulation that of the skeletal musculature predominates. Therefore, it is the nature and not the place of the stimulation that is decisive as to the organ most affected. In addition to the stomach, the small intestine and rectum, liver and gall-bladder are sensitive to touching with a hair. The elective heart action decreases caudad. The sensitiveness of the kidney and bladder is only moderate, that of the fallopian tube and ovary very slight. The parietal peritoneum is relatively insensitive. Stimulation of the skin and electric, thermal and chemical stimulation of the viscera only produced an irritant effect, if there was pronounced hypersensitiveness of the vagus, while there was always a reaction to mechanical stimulation of the stomach even when vagus sensitiveness was normal. Concentrically around the root of the mesentery there was a form of reaction for which apparently an adequate stimulus was furnished by tension of the tissues through traction. This sensitiveness may make possible a control of the motor processes in the gastro-intestinal tract by the sensory appreciation of changes in tension in the suspensory apparatus of the digestive tract brought about by the varying degrees of distension of the stomach and intestine in the course of digestion. This is a process analogous to deep sensation, which gives control of muscle activity and is a specific form of sensation in the viscera.

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**Studies on the Visceral Sensory Nervous System. XIII. The Innervation of the Cardia and the Lower End of the Esophagus in Mammals.**

*A. J. Carlson, T. E. Boyd and J. F. Percy, Am. J. Physiol., 61: 14, June 1, 1922.*

The authors wished to reinvestigate the subject of sympathetic  
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innervation of the cardia and lower esophagus in the dog, cat, and rabbit. Ether was used in all the crucial experiments during the preparation of the animal. To eliminate anesthesia and skeletal muscle contractions the authors employed decerebration, pithing the entire central nervous system, or the spinal cord below the level of the third cervical segment. In some experiments the chest was opened and the diaphragm isolated from the esophagus and cardia. A few experiments were made under a combination of ether and curare. Curare was found unsatisfactory since it induces a prolonged spasm of the cardia. The contractions of the cardia were recorded by a method illustrated and described in great detail. Briefly, it consists of the fixation of a balloon in the cardia and the connection of the two ends of the cardia balloon to separate water manometers, thus using the amount of the respiratory excursion through the cardiac end of the balloon as a measure of the tonus of the cardia. If the tonus or contraction of the cardia exceeds the pressure inside the cardia balloon, it is obvious that the balloon will be completely compressed in the cardia region, and the negative pressure in the chest produced by the inspiratory movements will be registered only through the esophageal end of the cardia balloon; and by raising the pressure in the balloon to a level at which the respiratory movements via the cardiac end are registered synchronously with those from the esophageal end, one has a measure of the strength of the cardia contraction. In all acute experiments the cardia and gastric balloons were introduced through a fistula in the stomach. After the apparatus was fixed in place the stomach was closed by silk sutures. The authors secured actual tracings to show (1) the relation of the tonus of the cardia to the tonus of the stomach; (2) the effect of section of the vagi nerves; (3) the motor and inhibitory action of the vagi on the lower esophagus and cardia; (4) the action of the splanchnic nerves on the cardia and lower esophagus; (5) possible sympathetic nerve supply to the lower esophagus and cardia other than that via the splanchnics; (6) the action of epinephrin on the cardia and lower esophagus; (7) the action of atropin on the vagi and sympathetic efferents to the cardia, and (8) the action of splanchnic nerves on the stomach. A study of these tracings shows that light anesthesia depresses the tonus of the cardia; deep anesthesia increases the tonus of the cardia. In the animal without anesthesia the tonus of the cardia runs parallel with that of the stomach. When gastric digestion is in progress the tonus of the cardia is high, even under anesthesia, and this hypertonus persists after removing the food from the stomach, washing the stomach cavity with water at body temperature, or rendering the stomach contents alkaline; 0.4% HCl in the stomach does not increase the tonus of the cardia parallel to that found in the digesting stomach. Under anesthesia, section of both vagi induces a cardio-spasm lasting usually from 3 to 15 minutes. The vagi contain both motor and inhibitory efferents to the cardia and lower esophagus (cat). On stimulation of the peripheral vagus the motor action prevails if the cardia is in low tone, the inhibitory action prevails if the cardia is in strong tone at the time of stimulation. The splanchnic nerves carry both motor and inhibitory efferents to the cardia and esophagus in the cat, in dogs only motor action, and in the rabbit only inhibitory action. Atropin abolishes both vagus and splanchnic action on the cardia

and lower esophagus. Epinephrin was found to have motor and inhibitory action on the cardia and esophagus in the cat and dog, inhibitory action only in the rabbit. The motor action of the drug appeared to prevail when the cardia was hypotonic, the inhibitory action when the cardia was hypertonic. On the stomach epinephrin had a predominantly inhibitory action in the cat and dog, a predominantly motor action in the rabbit. The splanchnic nerves, like the vagi, carry both motor and inhibitory efferents to the stomach. Splanchnic motor action on the duodenum was also noted. Carlson advances the tentative opinion that the reactions of visceral efferents (sympathetic and autonomic), at least on some visceral motor mechanisms, are association or reflex responses, and not simple peripheral responses like that of the skeletal muscles on stimulation of the pyramidal tract; that is the visceral efferent nerve fibers are in reality afferents to the local but diffuse reflex nervous centers in the visceral organs. He believes the prevailing view of antagonistic action of the vagus and the splanchnic systems is not tenable for the cardia and the stomach.

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**Pseudoparadoxical Pupil Dilatation Following Lesions of the Afferent Paths.**

*Joseph Byrne, Am. J. Physiol., 61:93. June 1, 1922.*

In studying paradoxical pupil dilatation induced by lesions of the afferent paths, the affected pupil was observed to exhibit at times a form of dilatation quite independent of the paradoxical phenomenon. As this appeared mainly during the preparadoxical and postparadoxical periods, the name pseudoparadoxical was applied and an independent investigation made, following the general method of study previously described by the author. The study was made (1) after section of one or more divisions of the fifth cranial nerve, (2) after crushing the posterior divisions of the upper cervical nerves, (3) after section of the muscles about the shoulder, (4) after section of the muscles about both shoulder joints and crushing of one brachial plexus, (5) after injury of one sciatic nerve, (6) after complete section of the posterior nerve roots, (7) after partial section of the posterior nerve roots, and (8) after excision of the posterior root ganglia. As a result of these experimental observations the author concludes that the dynamic factor in the mechanism resides in the bodies of the injured primary sensory neurones, and that the centripetal impulses immediately causing pseudoparadoxical pupil dilatation after sensory nerve lesions are the result of hyperfunctioning of the bodies of the injured primary sensory neurones. In the response of the sensory neurones to injury 3 stages are distinguishable of which the first and third are characterized by hyperfunctioning of the injured neurones (pseudoparadoxical phenomena) whereas the second or intermediate stage is characterized by hypofunctioning of the injured neurones and hypersensitivity of the related pupil dilator mechanism to adrenalin (true paradoxical phenomena). After sensory nerve injury the determining factor at any given moment between pseudoparadoxical or true paradoxical phenomena is the sum of the centripetal impulses emanating within a given time from the injured sensory neurones compared with the sum



of those emanating from the corresponding neurones of the sound side. When the impulses from the injured neurones overbalance those from the sound side, pseudoparadoxical dilatation ensues, but where the contrary obtains true paradoxical phenomena supervene. Part of the centripetal flow of impulses responsible for pseudoparadoxical dilatation passes to the brain where it inhibits the pupil constrictor mechanism, and part impinges upon the related half of the lower ciliospinal center of Budge where it augments the outflow of pupil dilator impulses via the cervical sympathetic nerve. The neurones of the nociceptive (affective) system are those fundamentally concerned in the mechanism of both pseudoparadoxical (hyperfunctioning) and true paradoxical (hypo-functioning) phenomena.

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**Further Studies of the Substances with Specific Action Produced by Different Organs. VII. Chemotactic Experiments on Paramecia and a Study of the Rapidity of Their Division under the Influence of Optons from Various Organs.**

*Emil Abderhalden and Olga Schiffmann, Pflüger's Arch. f. d. ges. Physiol., 194:206, Berlin, March 24, 1922.*

On the stage of a microscope a drop of a paramecium culture was placed and beside it one of an opton solution. A bridge was made between the 2 drops, and they were observed through the microscope to see whether there was a migration of paramecia into the second drop. Optons of corpus luteum, hypophysis, ovary, testicle, thyroid and thymus were studied. All these optons kill paramecia in strong concentrations; in lesser concentrations they attract them and in moderate concentrations have a negative chemotactic action. Solutions of 1:1000 of all the optons were preferred by the paramecia. Further experiments dealt with the effect of the optons on the rapidity of fission of the paramecia. In these experiments sometimes the descendants of a single paramecium were used. Such a strain, which corresponds to a pure-bred line in autogamous sexual reproduction, is called in recent literature on heredity a "clone." The use of such clones guarantees a uniform material, in which all the individuals are in the same phase of the rhythm of their fission. Optons from thymus and thyroid, which have the greatest influence on the development of tadpoles, hastened fission; with the former it took place on the seventh, with the latter on the fourth day. The opton of testicle also hastened fission, while those of the corpus futeum and hypophysis had an inhibitory action. These conditions are plotted in curves.

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**Further Experiments on the Effect of Endocrine Gland Substance on Morphogenesis.**

*Werner Schulze, Klin. Wchnschr., 1:896, Berlin, April 29, 1922.*

The thyroids of *Rana fusca* were extirpated in larvae. This could be completely done in only 6 of 25 cases; 4 of these 6 died of an accident and there was no further metamorphosis in the remaining 2. The incomplete extirpations resulted in normal or delayed metamor-

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phosis. One of the larvas with total extirpation was fed with beef thyroid and metamorphosis appeared. The other larva has lived for a year without metamorphosis. Other investigators obtained similar results after extirpation of the thyroid, the pituitary body, the pineal gland or the thymus. Moreover they produced giant growth by the feeding of thymus. There was hyperplasia of the thyroid when the thymus was removed and after thyroid extirpation there was apparently increased thymus function.

Schulze implanted in larvas of *Bombinator pachypus* in certain stages of development, thyroid of their own type, beef thyroid and normal and Basedow's thyroid of the human. This implantation hindered growth in size and increased the rapidity of metamorphosis. There was no difference in the effect of the different varieties of thyroid used. The breaking down of foreign thyroids was more rapid, but the rapidity in development with this form was greater. One case with implantation of the same kind of thyroid, developed a regular prolapse of the brain. This is of interest in the formation of such anomalies; the development may be considered as disturbed but not so much as in other experiments. Implantation of testicle substance had no influence on the development of the animal.

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#### **Pancreatic Extracts.**

*F. G. Banting and C. H. Best, J. Lab. & Clin. Med., 7: 464, May, 1922.*

The facts brought out by Ibrahim and Carlson, coupled with the evidence afforded by the previous experiments of the authors, suggested the possibility that the fetal pancreas might prove a source of an extract rich in internal secretion and yet free from the destructive enzymes of pancreatic juice. To test this hypothesis, a quantity of pancreas was obtained from fetal calves of less than 5 months' development. The tissue was macerated in Ringer's solution, and the liquid filtered off. The filtrate was tested on several different diabetic dogs and it produced similar effects upon the percentage sugar of the blood and on the sugar excreted in the urine, as did the extract prepared from degenerated pancreatic tissue. The extract was not found to contain any proteolytic enzyme.

Two experiments are reported in which such extracts of fetal calf pancreas were used on pancreatized dogs. These observations were partly to determine whether extracts having an antidiabetic power equal to those prepared from the degenerated pancreas could also be prepared from the normal gland, and partly to find out whether frequent injection with active extracts would prolong the life of a depancreatized animal beyond the limit of time which such animals ordinarily survive.

The conclusions are that by intravenous and subcutaneous injections of neutral saline extracts prepared from the pancreas of the bovine fetus at about the fifth month, the percentage of blood sugar and the daily urinary excretion of sugar are markedly reduced in depancreatized dogs. Daily injections of extract of pancreas enabled a depancreatized

dog to live 70 days. The active (antidiabetic) principle of such extracts is destroyed by boiling in a strongly acid solution but it is not affected by the presence of tricresol which may therefore be used as a preservative. The depressor action of the extract is short-lived.

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**Hormonal Sterilization of Female Animals by the Subcutaneous Transplantation of Ovaries of Pregnant Females.**

*L. Haberlandt, Pflüger's Arch. f. d. ges. Physiol., 194:235, Berlin, March 31, 1922.*

During pregnancy the corpus luteum develops and acquires internal secretory functions, but at the same time the interstitial tissue of the ovary increases, especially from the time at which regressive changes begin in the corpus luteum. It may be assumed that these interstitial cells take over the functions of the corpus luteum, as well as its capacity for inhibiting ovulation. As in transplanted ovaries there is a pronounced increase of interstitial cells, a study was made to determine whether the subcutaneous transplantation of ovaries of pregnant animals, as a result on the one hand of the implantation of corpus luteum and on the other of proliferation of interstitial tissue, would bring about a temporary sterilization of the host animal, by inhibiting the maturation or rupture of the follicles into its own ovaries. The experiments were made on 8 rabbits and 8 guinea-pigs. The fascia being removed, ovaries were implanted under the skin of the back on a bed of muscle which had been freshened up. In the implanted ovaries or ovarian rests, after 1-10 months, the interstitial tissue was preserved and represented the greater part of the organ. The follicles, only a few of which were preserved, had undergone atresia. Therefore, it was primarily the interstitial cells of the transplanted ovaries that were responsible for the temporary sterility of the experimental animals. This tissue must have greatly increased in amount, as the size of the implanted organ 3 months after implantation was considerably greater than it was at the time of operation. While in the first part of the experiment it is the corpora lutea of the implanted ovaries that inhibit ovulation, in proportion as these undergo retrogression the interstitial tissue takes over vicariously this function. In further experiments opton made from corpus luteum was injected. In 5 of the 8 rabbits in which implantation experiments were made, there was sterilization for varying periods of time—up to 3 months with 15-21 intercourses. Of the 8 guinea-pigs, 4 were negative. The injection experiments were all negative, probably because the opton was not prepared exclusively from pregnant animals.

It might be determined whether these experimental results could be used in practical medicine where it is desirable to sterilize a woman temporarily without operation. Injections of extracts of corpus luteum of pregnant animals might be used, for example of cows, as experience has not shown that the action of these extracts is confined to the same species; it is possible that administration by mouth might be effective. The cessation of menstruation when ovulation is inhibited might result in atrophy of the uterus, and therefore the sterilizing treatment should be intermittent. The author calls attention to the



analogy between the epithelial cells of the corpus luteum and the connective tissue, epithelioid, interstitial cells (theca-lutein cells), which are properly included under the common name of lutein cells. It is probable that they are both developed from the same material. The sterilization treatment would, by reason of the development of theca-lutein cells in the obliterated follicles, cause a greater degree of inhibition of ovulation than is the case in pregnancy. The inhibition of ovulation does not do any harm to the ovaries of the experimental animals, as is shown by the fact that they later became pregnant; it is a temporary sterilization that afterward disappears completely.

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**The Functional Relationship between the Gland Parenchyma of the Ovary and the Cortex of the Suprarenal.**

*M. G. Sserdjukoff, Virchow's Arch. f. path. Anat., etc., 237:154, Berlin, March 18, 1922.*

The author first gives a review of the literature upon the physiologic relationship between the gland parenchyma of the ovary and the cortex of the suprarenal. He tried to disturb the correlation between the suprarenals and ovaries in pregnant and nonpregnant cats by excluding the ovaries and then the suprarenals, and came to the following conclusions: (1) There is a functional interdependence of the secretory function of the suprarenal cortex, the parenchyma of the corpus luteum and the interstitial gland of the ovary. (2) This functional relationship is manifested by changes in secretory cells, which, as shown by these experiments, play a vicarious rôle among the three glands. (3) The functional synergy between the cortex of the suprarenal, the parenchyma of the interstitial gland and of the corpus luteum, is indicated by the lipid character of their secretion. (4) When there is a disturbance of the secretion of the interstitial gland the production of lipid secretion increases in the suprarenal cortex, and vice versa. (5) As a result of the great and varied significance attributed by present-day physiology to the lipoids in biochemical processes, further studies of the physiological action of the lipid secretion of the suprarenal cortex, the interstitial gland of the ovary and of the corpus luteum, is very desirable, as the theory advocated by some authors of the negative secretion of the suprarenal cortex, the antitoxic action of the cortex, etc., undoubtedly requires confirmation and some proof based on facts, and the whole question demands revision.

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**A Method of Artificial Perfusion of the Spleen.**

*Emil v. Skramlik, Pflüger's Arch. f. d. ges. Physiol, 194:118, Berlin, March 24, 1922.*

The technically difficult task of perfusion of the excised spleen is best accomplished in the sheep, in which the spleen is a rectangular organ without a true hilum and the artery, vein and nerve enter at one corner. After bleeding the animal, the abdominal cavity is opened, the rectum and esophagus ligated, and by incising the root of the mesentery  
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the gastro-intestinal tract is removed along with the liver, spleen and pancreas. In this preparation, after complete bleeding and irrigation, the spleen is perfused rhythmically. The conditions are much more complicated in the dog's spleen, because its vessels give off numerous branches to neighboring organs.

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**Studies of the Parathyroid Apparatus. V. The Significance of the Comparative Mortality Rates of Parathyroidectomized Wild Norway Rats and Excitable and Nonexcitable Albino Rats.**

*Frederick S. Hammett, Endocrinology, 6: 221, March, 1922.*

Three groups of rats were used for these experiments, "stock albinos" (normal animals showing low threshold of response to stimulation and high muscle tonus); "gentled albinos" (in which excitability and muscle tone had been reduced to a low level by constant handling and petting); untamed wild Norway rats caged for 1 or 2 generations. The first paper dealt with the comparative mortality in the first two groups, the present study deals with the last group. Parathyroidectomy was done on 102 rats; of these 92 died within the standard period (48 hours). All except 3 showed tetany. In gentle albino rats the mortality had previously been shown to be 13% and in untamed albino rats, 79%. The high mortality is regarded as correlated with heightened neuromuscular activity and resultant augmented toxin formation.

Crile has shown that the emotional trend of the individual is an important factor in the degree of resistance to disturbing conditions. Hammett believes that not only does the bodily constitution affect the functioning of the nervous system, but also that the neural activities have a profound effect upon bodily constitution. Of the three current theories of cause of the tetany in animals after parathyroidectomy (calcium deficiency, disturbance of acid-base equilibrium of blood; toxemia due to the presence of a guanidin compound from protein catabolism), the author's observation favor the toxemia theory.

His working hypothesis is best defined in his own words: From the observations on the 3 groups of rats certain general conclusions of practical significance can be drawn. It is evident that the more excitable the organism the higher is the neural and muscular tension, the greater is the instability, the greater is the production of toxic by-products, the greater is the need for the mechanism for getting rid of these poisonous substances and the greater is the dependence of the organism on the parathyroids in averting disturbances arising from these sources.

The protective function of the parathyroids apparently is of decreasing importance as the tendency for acceptance of environmental changes without protesting response is increased. The result of the diminution of the domination of the emotions of fear and anger, which as Hall points out is a major impelling motive of man, is a lessening of the production of organic changes which are detrimental to the individual. Resistance is raised. It would appear as if Crile, in his custom of having his patients undergo a preliminary period before operation in which they are familiarized with the procedure of

anesthesia and in which by education fear is lessened, has been putting into practical use the principles which these experiments on excitable and gentled albino rats seem to establish.

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## 1b. BIOLOGIC AND ORGANIC CHEMISTRY.

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**Hysteresis of Protoplasm and a Method for Its Direct Determination.**

*Vlad. Ruzicka, Pflüger's Arch. f. d. ges. Physiol., 194: 135, Berlin, March 24, 1922.*

In the early epochs of development which led to the formation of independent morphologic structures, the chromatic parts of the cell were in relative predominance, while in later periods the achromatic parts (plastin) predominated. Structures rich in plastin are in a physiologic sense relatively quiescent (spores and resting nuclei), while those rich in chromatin are relatively active. This is a question of physicochemical transformation of biocolloids, of a transition from a labile (highly dispersible) into a stabile (slightly dispersible) condition. Aging is also due to such a transition into a stabile condition, which in this case is irreversible. Evidently the time factor is a cause of change in the condition of aggregation of living substance, and the movement is in the direction of increased concentration. The condensation of living substance the author terms hysteresis of protoplasm and the life processes caused by it he terms hysteretic processes. Hysteresis increases constantly in the course of the ontogenetic and strophogenetic development of the frog. It is natural to see in it an analogy with the hysteresis of colloids; the change in the physical properties of a colloid that takes place with time is a decreased capacity for dialysis. To confirm this analogy it is necessary to prove that the flocculability of the biocolloids of old cells is increased as compared with that of young cells. It is known that there are differences with reference to diffusibility, elasticity, edematization and water content, which decrease with time. The degree of condensation or aggregation may be examined by direct determination of solubility. Experiments on tadpoles of different ages, from the same mass of spawn, showed that solubility in trypsin decreases with advancing development. Other methods are the determination of the pH, the demonstration of internal friction, the demonstration of osmotic pressure, electro-endosmosis and flocculability. In order to study this, the material to be examined was cut in pieces, pressed, the tissue fluid diluted, filtered and dropped from a burette into 96% alcohol. The composition of older tissues and fluids was nearer the iso-electric point than that of younger ones. It is well known that the distance from this point determines the condition of aggregation. It is thus demonstrated that time increases the condensation hysteresis of living substances, a fact which makes it necessary to supplement Hering's scheme of metabolism (assimilation-dissimilation) by the introduction of hysteresis and which also shows that the second main proposition of thermodynamics holds good for

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living substance. Hysteresis shows that metabolism is not a reversible process, and must necessarily lead to natural death, as it strives toward a resting condition, a maximum of entropy. The fact of hysteresis shows that a complete regeneration, i. e. a complete return to an earlier condition, is not possible. Practically this may be of value from the standpoint of legal medicine. A whole series of questions appear in a new light from this point of view and should be gone over again; these include the "immortality of the protista," the relations of metabolism to morphogenesis, the problem of rejuvenation, the tumor problem, the question of growth and cell maturity, sexuality, inheritance, the effect of inbreeding.

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**Physical Conditions for Hysteretic Changes.**

*Erwin Bauer, Časop. lék. česk., 61 : 345, Prague, April 22, 1922.*

In the course of ontogeny, there is an increase of protein combinations of great molecular complexity which possess very slight intumescibility, and which are almost insoluble (plastin, keratin, connective tissues). This increase is at the expense of the protoplasm in the form of colloidal suspension. The formation of these more stable substances runs parallel to the intensity of the metabolism, or in general to the intensity of function. In every organism there must always be the possibility of change according to definite conditions. Free energy can fall only to a certain positive minimum; the entire increase of total energy must be applied to the regulative functions. Electric energy, for example, whose quantity, i. e. the mean of the potential difference and the total charge of the organic colloids, is determined by the colloidal condition of the living system, cannot remain constant, but is always changing; it can, however, increase only up to a certain limit, the "limit of assimilation," and must sink again within a certain limit. This increase causes a diminution of the difference of electric potential, but this diminution can reach only a certain "limit of dissimulation." The total electric energy of the organic colloids depends on the size of the limiting surface, which in turn depends in large part on the dispersion phase, on the degree of the dispersion and potential difference at the limiting surface. There can be no dynamic equilibrium as this energy changes with every function of life (assimilation, etc.) and for this reason either the potential difference must fall or the limiting surface must diminish. The product of the work accomplished in this way must increase, i. e. the degree of dispersion, or the potential difference, or perhaps only up to a maximum limit; after a certain time it must decrease in the course of ontogeny. The work output of the organism must fall to a certain limit only, the potential difference at the limiting membrane must not surpass a certain value, if the organism is to remain alive; in other words, if the potential difference departs from certain limits, it leads to the death of the living system. Every growth or assimilation process which is concerned with actual increase of the total energy of the organism leads to a diminution of the degree of dispersion and of the difference of electric potential at the limiting surface. Moreover, if this process ceases, however, a constant (although retarded) decrease of the poten-

tial difference and the stability of the organic colloids invariably follows. These experiments can be corroborated by Ruzicka's work.

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**Experiments with Vital-Lethal Staining in Relation to Hysteretic Processes.**

*Erwin Bauer, Časop. lék. česk., 61:393, Prague, May 6, 1922.*

A vital-lethal stain is one to which living and dead cells react differently, by which it serves to give information as to the difference between living and dead protoplasm. Ruzicka's method depends on the fact that a mixture of neutral red and methylene-blue stains living cells red, but this color changes to blue if the cells die. The staining with neutral red is a true vital reaction which is dependent on unaltered functioning of the cell, but no exact information is available to explain why the plasma takes a red stain during life and what factors (lost at death) determine the blue stain. As the solutions of the stains are invisible under the microscope in the concentration occurring in the cells, the staining of a cell cannot be due to simple absorption of the dye.

There are 3 possibilities: (1) The dissolved stain forms a chemically insoluble combination with certain portions of the plasma. (2) The dissolved stain forms a precipitate on the surface of the plasma. 3. The stain is absorbed on the surface and appears as a concentrated solution at this place. Hence it is not correct to assume that stains which are invisible after injection into the body have not penetrated the cells. Ruzicka's stain can only be explained on the basis that the methylene-blue is present in the living cell but in an invisible form. Experimental studies may determine which of the 3 aforesaid possibilities is correct. This bears a relation to hysteresis. Both stains enter the living cell, but since red has a lower electric charge, it forms a precipitate on the portion of the plasma with a higher electric charge. The plasma loses its charge at death and the electric affinity disappears, the red color again dissolves in the plasma and in its place the methylene-blue is concentrated, just as occurs on all limiting surfaces. This explanation involves 3 factors, all of which have been demonstrated: (1) The electronegative colloid actually prefers the dye (red) with the lower electric charge in a mixture of neutral red and methylene-blue. (2) The red is again dissolved when the electronegative colloid has lost its charge. (3) Methylene-blue is absorbed if there is no charge at the limiting surface.

This does not necessarily imply that oxidation or reduction processes are not also involved in these changes nor that these do not aid in the appearance and disappearance of the stain.

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**Photographic Estimation of the Concentration of a Staining Solution.**

*W. R. Hess, Hoppe Seyler's Ztschr. f. physiol. Chem., 119:172, Berlin, April 20, 1922.*

Estimation of the concentration of a staining solution by photo-  
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graphic records represents a considerable increase in delicacy, especially for yellow, toward which the eye is very insensitive in intensity evaluation. Photographic colorimetry also yields results that may be re-examined at any time and enables color intensity to be estimated with an indicator not subject to any disturbing influences. The apparatus consists of a scale having superposed fields of graduated brightness. The lowest field is white while the uppermost, specially adapted for the purpose, is more or less dark. The height of the individual field is 2.5 mm. and the width about three times as great. The scale is itself prepared photographically by means of graduated exposure of very thin mat paper. After preparation it is fixed on a glass plate. In its center a strip 2.5 mm. wide is cut out of the paper. The fissure, beneath which the surface of the glass plate is exposed, cuts all fields vertically. Photographic exposure is made on a cinematograph film. The method is specially advantageous in serial examinations. It is applicable to the most diverse staining solutions and particularly to those whose absorption lies in the left half of the spectrum. All exposures that are to be compared must be carried out with the same grade of plate, film or paper.

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#### **Surface Energy in the Origin and Manifestation of Movements of Living Cells.**

*Erwin Bauer, Časop. lék, česk., 61: 372, Prague, April 29, 1922.*

Recent observations on the function of surface tension in the origin of form and movement assume that all cells forms are in a state of equilibrium and that a deviation from this balance is caused by local influences which again allow the altered equilibrium to be considered as balanced forms. This principle assumes that the living cell cannot counteract the effect of surface tension. This surface tension of the cell depends on the surrounding medium. This does not account for the rôle of surface energy in the energy exchange of the cell and in the causation of other forms of cellular activity. The author attempted to alter the surface tension by changing the medium in order to observe how living cells react. Unicellular organisms *Paramecium* living in water proved suitable for such experiments, and cholates were used to change the surface tension of the water. Solutions of sodium glycocholate of various strengths were added in increasing amount to a drop of water containing *Paramecium*. There was no change in the form or condition of *Paramecium* several hours after addition of a 2% solution. The same was true immediately after addition of a 4% solution but changes appeared after thirty minutes which could be observed by passing a galvanic current through the fluid. The changes consisted of an increase in width and decrease in length, slowing of the movements and eventually complete rest. There were also twists in the long axis followed by sacculation with rupture of the microorganisms at these points. The same changes occurred earlier in stronger solutions. It is certain that this effect is due to diminished surface tension. It cannot be due to osmotic pressure because this would produce a reversed effect (contraction in higher concentration and vice versa).

The results show: (1) Living cells can activate other powers against the effect of surface tension in order to prevent the formation of a balance form and thus to maintain the differences in tension. (2) The reaction of Paramecium to the direct electric current is a result of decreased surface tension as exactly the same reaction can be produced by direct reduction of the tension without the current.

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**An Apparatus for the Rapid Measurement of Surface Tension.**

*Robert G. Green, J. Bacteriol., 7: 367, May, 1922.*

The apparatus known as a surface tension balance was designed for rapidly measuring the surface tension of liquids by the drop-weight method with an accuracy consistent with ordinary experimental conditions. The apparatus consists of 3 mechanical parts: a dropping pipet, a balance-beam mounted on a torsion wire, and an adjustable scale upon which the surface tension is read directly in dynes. The weight of a drop of liquid falling from the pipet into the cup attached to the end of the balance-beam is proportional to the surface tension of the liquid. The surface tension balance is first calibrated with a standard liquid of known surface tension and the adjustable scale moved to coincide with this reading. When the unknown liquids are used the readings of the scale give their corresponding surface tension.

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**Modern Ideas Respecting Acidity and Alkalinity.**

*F. W. Gamble and Norman Eves, Lancet, 202: 1076, London, May 27, 1922.*

Litmus, as compared with the newer synthetic substances, is a bad indicator of acidity and alkalinity. The more recent means for determining pH are the outcome of the electrometric methods. The strength of an acid depends entirely on the number of H-ions present in a certain volume of its solution, i. e. on the pH not on the amount of acid present. The latter is determined by titration. Similarly, bases depend for their properties on the number of hydroxyl (OH) ions present, the number of such ions present in solutions determining the strength of a base. Pure water is neutral, containing about a billion OH-ions and a billion H-ions per liter. It is usual to speak of the pH of all solutions, whether alkaline or acid, and the HO-ion concentrations can be calculated therefrom. The concentration of solutions is expressed in terms of a normal solution, which contains in liter, an amount of the substance corresponding to gram-atom of hydrogen (i. e., 1.008 gm.); pH is expressed in the same way, and therefore, a normal concentration would be 1.008 gm. of H-ions per liter. Points to bear in mind in regard to pH values are: (1) the higher numerical value of pH the lower becomes the H-ion concentration, and (2) altering the pH value by 1 integer, the H-ion concentration is altered 10 times. Acid solutions have pH values of less than 7, and those greater than 7 are alkaline. To obtain OH-ion concentration, or pOH, subtract the pH value from 14.



A generally useful process of determining H-ion concentration is by means of the colorimeter, or indicator method, the data for which are obtained by comparison with the electrometric standards. The color change should be sharp, the two end colors forming as much of a contrast as possible. Another essential of a good indicator is that it should be affected as little as possible by the presence of neutral salts or other compounds. The first requirement for the use of the indicator method is the preparation of solutions of standard pH from salts which show buffer action, as sodium phosphate, since such solutions are comparatively unaffected by outside influences. Instead of using a number of indicators, each covering a certain pH range, it is often convenient to use a suitable mixture of indicators covering a much wider range. A compound indicator, devised by J. L. Lizius, shows color changes through the spectrum from red to violet over the wide range of pH from 4 to 11. A small tablet, containing a definite amount of this indicator, is dropped into 10 c.c. of the solution to be tested and in about 1 minute gives a definite color to the solution. One is thus able to determine the pH by a test as easily applied as the ordinary litmus test.

The value of determining the pH is that all living organisms or cells, moulds, yeast, bacteria, etc., have a definite pH at which maximum growth proceeds, and in laboratory work the medium should be at the optimum reaction for their growth.

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**The Ionometer. A Simple Clinical Method for the Determination of the Conductivity.**

*Johanne Christiansen, Wien. klin. Wchnschr., 35:461, May 18, 1922.*

The voltmeter is connected with the U-shaped tube and the contact of the direct current of the city supply. Platinum electrodes are soldered to the tube. The length of the U-shaped capillary tube is 10 cm. and the diameter 1.8 mm. A small quantity of blood serum is poured in. The U-tube is placed in water at 18° C. The contact is turned and the deflection of the indicator of the voltmeter, which depends only on the resistance of the solution in the U-tube, provided the city current delivers a constant quantity of volts, is read off. This deflection is not proportional to the conductivity of the solution. An empiric table or curve must be constructed for every tube by using salt solutions of known conductivity at 18° C. (the temperature chiefly used in the best conductivity tables). Such a table is rapidly made, as each determination takes only a few minutes.

There are only 2 sources of error: (1) The temperature must be kept exactly at 18° C. because the temperature coefficient of the conductivity is very great (about 2%). (2) The voltage of the city current must be kept constant; this may be accomplished in various ways. In the apparatus made by Helweg-Mikkelsen of Copenhagen, there is a magnetic "shunt," an iron plate which can be screwed on and off and which changes the magnetic field of the voltmeter. The U-tube is removed and the voltmeter is set at a given point, by means of this

shunt, before and after every determination. The U-tube described has a volume of 0.5 c.c. and can be used for urine or blood serum. A larger tube of about 50 c.c. volume must be used if very slight conductivities are to be measured, as in water analyses.

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**Estimation of Hydrogen-Ion Concentration in Urine with Indicators.**

*Adolf Silberstein, Biochem. Ztschr., 128:534, Berlin, March 28, 1922.*

The color interferes with the estimation of H-ion concentration in urine by indicators. Soerensen gave the following directions in such a case in *Biochem. Ztschr.*, 21:139, 1909, and 22:352, 1909: "The comparison solutions are given the same color tone as the experimental solution with the aid of Bismarck brown; adequate addition of indicator solution is necessary to conceal unavoidable small differences. In case the experimental liquid is turbid a similar turbidity is imparted to the comparison solutions by adding a barium sulphate suspension." Herein, however, errors may arise owing to uncorresponding agreement with the comparison solution. To exclude these errors the urine to be tested was previously shaken with animal charcoal and filtered. This modification would not be applicable if the negatively charged particles of the charcoal suspension fixed the positive ions of the salt solution at its surface; in that case unequal adsorption of differently charged particles would take place and the urine's hydrogen exponent would be different before and after agitation with animal charcoal. The experiments showed, however, that the urine's hydrogen exponent is not affected. The difficulty of applying the indicator method to the estimation of the hydrogen exponent of colored liquids may be overcome by this simple modification. The method represents a material simplification of the indicator method of estimating H-ion concentration in urine.

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**The Elimination of Discrepancies between Observed and Calculated Potential Difference of Protein Solutions Near the Iso-Electric Point with the Aid of Buffer Solutions.**

*Jacques Loeb, J. Gen. Physiol., 4:617, May 20, 1922.*

The author noticed in his previous experiments on the influence of the hydrogen ion concentration on the P. D. between protein solutions inside a collodion bag and aqueous solutions free from protein that the agreement between the observed values and the values calculated on the basis of Donnan's theory was not satisfactory near the iso-electric point of the protein solution. It was suspected that this was due to uncertainty in the measurements of the pH of the outside aqueous solution near the iso-electric point. With the use of buffer solutions as described in previous papers this discrepancy disappeared, proving that the suspicion was correct.

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**The Living Cold-Blooded Animal as an Indicator of Changes in Colloidal Condition.**

*Hans Molitor and Ernst P. Pick, Klin. Wchnschr., 1:787, Berlin, April 15, 1922.*

Experiments with frogs showed that these animals can be kept in water or in 2% hypertonic salt solution without any marked change in weight, but that the introduction of substances that cause a change in the colloidal equilibrium of the tissues alters the water exchange of these animals and therefore the weight. When Ringer's solution was injected, this was excreted within twenty-four hours by the animals, but when Straub's normosal solution was injected there was an increase in weight for eight days, which was followed by a loss of weight to considerably below normal. This shows the different action of these two solutions on the water exchange of the tissue colloids. Other colloidal systems, such as starch, gelatin, blood serum and even products of protein catabolism, also affect the water exchange of the frog when introduced into the lymph sac or the circulation of the animal.

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**Urinary Colloids and Their Estimation by the Gold Number Method.**

*B. Ottenstein, Biochem. Ztschr., 128:382, Berlin, March 28, 1922.*

Colloids possess slight capacity for diffusion. Colloidal substances present in urine must have passed through the membrane of renal epithelium. The quantitative estimation of urinary colloids and their pathologic increase was effected by stalagmometry or by Zsigmondy's gold number method. By the gold number of a colloid is understood that number of milligrams which is no longer capable of protecting 10 c.c. of a bright red gold sol, containing 0.0053-0.0058% metal, against the coagulating action (color change to violet) of 1 c.c. sodium chlorid solution (100 c.c. sodium chlorid to 900 c.c. water). Ordinarily the change from red to violet takes place immediately or within a brief time. It was attempted to ascertain whether a quantitative difference in urinary colloids could be determined in the urine of different patients by the gold number method. The method was carried out as follows: A series of sterile test tubes receive 1, 2, 3, 4, etc., c.c. of the dialyzed urine. To each tube 2.5 c.c. of the red gold sol is added, the solutions are shaken strongly and allowed to stand three minutes, and 1 c.c. of 4% sodium chlorid solution is added to each tube. By systematic comparison of the mixtures in which no color change with those in which such a change took place it can be determined exactly what quantity of urinary colloids just suffices to prevent the change to violet. The final reading is taken after two hours. The gold number is calculated by determining the percentage of colloidal substances in the dialyzed urine by evaporating 50 c.c. of the dialysate on the water bath. The number of cubic centimeters multiplied by the number of milligrams of colloidal substance contained in 1 c.c. yields the gold number.

Examinations were made of normal urine (having regard to diet), urine of tuberculous patients and those with carcinoma, Basedow's

disease, pneumonia, asthma, arthritis, melancholia, dementia praecox, epilepsy, paralysis and psychopathy. The experimental results are summarized in a table from which it appears that the gold number varies between 7.0 mg. and 3.5 mg. in normal urine, independently of the concentration and reaction. In tuberculous individuals the gold number was less, so that considerable colloidal substances were present in the urine. In carcinoma cases increase of urinary colloids could be observed in only 1 case. In a gouty individual after atophan treatment the gold number was 20 mg. (very high); later normal values were obtained. Pneumonia, Basedow's disease and bronchial asthma gave unequal values. In the aged, mental, epileptic and paralyzed patients no appreciable variations from healthy individuals were shown. The gold number was usually higher than 15 in degenerates and psychopaths. Regarding the nature of the colloidal substances in urine nothing can be said, nor has it been possible to determine why more colloids are normally secreted in males than in females. Possibly differences in the permeability of membranes play a part.

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**Electric Charges of Colloidal Particles and Anomalous Osmosis. II. Influence of the Radius of the Ion.**

*Jacques Loeb, J. Gen. Physiol., 4: 621, May 20, 1922.*

The author found that when solutions of KCl, NaCl, or LiCl are separated from water without salt by a collodion-gelatin membrane and when the pH of both salt solution and water is on the acid side of the iso-electric point of gelatin, water diffuses from the side of pure water into the salt solution at a rate increasing inversely with the radius of the cations. The adsorption theory would lead one to assume that this influence of the cations is due to an increase of the potential difference between the liquid and the membrane inside the pores of the gelatin film of the membrane, but direct measurements of this potential difference contradict such an assumption, since they show that the influence of the 3 salts on this P. D. is identical at pH 3.0. It was found, however, that the P. D. across the membrane is affected in a similar way by the 3 cations as is the transport of water through the membrane. This potential difference across the membrane varies inversely as the relative mobility of the 3 cations which suggests to the author that the influence of the 3 cations on the diffusion of liquid through the membrane is partly if not essentially due to a diffusion potential.

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**Studies on the Regulation of Osmotic Pressure. II. The Effect of Increasing Concentrations of Albumin on the Conductivity of a Sodium Chlorid Solution.**

*Walter W. Palmer, Dana W. Atchley and Robert F. Loeb, J. Gen. Physiol., 4: 585, May 20, 1922.*

The authors have previously shown that the addition of gelatin in increasing concentrations to a 0.6% sodium chlorid solution affects the conductivity in two ways, depending on the H-ion concentration. At  
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pH 3.3 the conductivity increases with each added increment of gelatin, whereas at pH 5.1 and 7.4 the conductivity decreases as the percentage of gelatin increases. In this paper the authors present similar experiments with another protein—egg-albumin. A preliminary determination of the conductivities of pure egg-albumin solutions varying in concentrations from 0.8 to 8.7% was carried out as in the case of gelatin. The first experiment was performed with pure albumin solutions varying from 1.1 to 8.3%. The conductivity of these solutions was determined at pH 3.1, 5.3, and 7.3. The results are plotted in Fig. 1 in the article with the concentrations of albumin as abscissae and the specific conductivities  $\times 10^{-4}$  as ordinates. In the second experiment gradually increasing amounts of albumin were added to a 0.6% NaCl solution. Observations were made at pH 3.5, 5.0 and 7.3. In Fig. 2 the results are plotted on a common scale, conductivities as ordinates and concentrations of albumin as abscissae. It was found that egg-albumin, like gelatin, influences the conductivity of a 0.6% NaCl solution in two ways: (a) at an H-ion concentration of about pH 3.0, increasing concentrations increase the conductivity; (b) near the iso-electric point of albumin and at the pH of the blood, increasing concentrations of albumin decrease the conductivity of the NaCl solution.

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**On the Equilibrium Condition between Blood Serum and Serous Cavity Fluids.**

*Robert F. Loeb, Dana W. Atchley and Walter W. Palmer, J. Gen. Physiol., 4: 591, May 20, 1922.*

The authors made a study of several physicochemical properties of blood-serums and edema fluids simultaneously obtained. The cases included heart disease and nephritis with ascites, hydrothorax, and subcutaneous edema; cirrhosis of the liver with ascites; and tuberculous pleurisy with effusion. The determinations on the blood-serums and edema fluids included freezing-point depression, specific conductivity, Cl,  $\text{HCO}_3$ , Na, K, glucose, nonprotein nitrogen, protein per cent (by Kjeldahl and refractivity) and, in certain cases, urea and Ca. The tabulated results show that the following relationships between blood-serum and edema fluids are apparently constant: (1) The freezing-point depression of serum and of edema fluid is the same—within the limit of error of the method when applied to physiologic solutions. (2) The conductivity of the edema fluid is always higher than that of the blood, but the greater the protein content of the edema fluid, the closer the conductivity approaches that of the serum. (3) The chlorid content of the edema fluid is always higher than that of the serum. This difference of Cl concentration in blood and edema fluids diminishes, in general, as the protein content of the edema fluid increases. (4) The concentration of potassium is greater in the serum than in the edema fluid. (5) The concentrations of  $\text{HCO}_3$ , sugar, Na, nonprotein nitrogen, and Ca and urea, where these were determined, were found to be approximately the same. The experiments on the dialysis of serum against edema fluid reported in the article, demonstrate that no new equilibrium is established when the 2 fluids are separated by a simple collodion membrane.



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**Plasmolysis and Permeability.**

*Silvester Prat, Biochem. Ztschr., 128:557, Berlin, March 28, 1922.*

The plasmolytic method of measuring cell permeability was perfected by Fitting and Hoefler, but it is often impossible to determine whether the increase in protoplasmic volume by permeability is not affected simultaneously by exosmosis. The capacity of the nucleoplasm to swell up seems to vary and the plasmometric method appears to depend not merely on conditions of permeability (velocity of penetration) of the plasmolytic agent, but on the final result of different interacting processes. The experiments were carried out with *Spirogyra*. Standard solutions of the salts were prepared. All measurements were conducted at 18-22° C. The cells were drawn by Abbe's drawing apparatus before being measured. Experimental results are recorded by curves and were as follows: The degree of plasmolysis increases after a definite time in univalent ions while it remains constant or decreases continually in bivalent ions. This action is characteristic both for cations and anions but the cation effect predominates. The course of plasmolysis is illustrated by the series  $K > Na > Ca > Mg$  for cations and by the series  $NO_3 > Cl > SO_4$  for anions. Changes in the degree of plasmolysis cannot, however, be referred simply to ability to pass within. In addition to exosmosis the degree of hydration of the plasma colloids, enzymatic cellular processes and other factors have to be considered. Premortal increase in permeability could not be detected plasmometrically; on the contrary, a fall in the degree of plasmolysis was frequently observed before death even in univalent ions. Anilin promotes the staining of *Spirogyra* by methylene-blue and neutral red, and vital staining of tannins by  $FeSO_4$ ,  $NaH_2PO_4$ , but induces decrease of the degree of plasmolysis ( $NaCl$ ,  $KCl$ ) in plasmometry.

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**Studies of Hemocyanin. IV.**

*Ch. Dhéré and A. Schneider, J. de physiol. et de path. gén., 20:1, no. 1, Paris, 1922.*

The hemocyanin examined was derived from the following species: *Helix pomatia*, *Octopus vulgaris*, *Octopus macropus*, *Eledone moschata*, *Palinurus vulgaris*, *Homarus vulgaris* and *Astacus fluviatilis*. Oxyhemocyanin was tested with hydrogen, nitrogen and carbon dioxid. Hemocyanin, reduced from oxyhemocyanin, was examined with carbon monoxid, nitrogen dioxid, methane, ethylene and acetylene. In the authors' technic, all reducing influences except the action of the inert gas were rigorously excluded, and all the gases employed were absolutely free from oxygen. Reduction was indicated by the disappearance of the blue color. It may be accomplished as readily by exposure to an inert gas at 15°-20° C., as by use of a vacuum at 40° C. Pure crystallized oxyhemocyanin was employed. In nearly all the tests, reduction was obtained in the presence of an antiseptic (boric acid, sodium fluorid). The leukocytes were filtered out. The reducing effect appeared in a few minutes and was complete in fifteen to thirty minutes, according to the rapidity of the gaseous current. Total reduction was

obtained by accelerating the rapidity of the gaseous flow. Foaming is indispensable for rapid reduction. Determination of the exact moment of complete reduction is sometimes difficult, on account of opalescence. This difficulty may be largely avoided by using crystallized hemocyanin which is very fresh. Each test should be checked by restoring the blue color by aërating the liquid. Oxyhemocyanin is functionally equivalent to oxyhemoglobin. The oxygen compounds formed are similar and governed by the same physiochemic laws. The authors have not examined the hemocyanin of *Limulus*, but it probably behaves like the hemocyanin of mollusks. The name hematinocyanin is suggested for the copper radical which fixes oxygen. However, nothing is yet known of the reactions of the copper group. From the standpoint of utility, hemocyanin is superior to hemoglobin in that it combines loosely, or not at all, with carbon monoxid.

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#### **Studies of Hemocyanin. VII.**

*Ch. Dhéré and A. Schneider, J. de physiol. et de path. gén., 20: 34, no. 1, Paris, 1922.*

In another series of experiments, crystallized oxyhemocyanin, dissolved in 0.02 n. sodium carbonate, was treated with nitrogen dioxid, methane, ethylene and acetylene. With nitrogen dioxid, hemocyanin forms a green, crystallizable pigment, which may decompose, but which is more stable than oxyhemocyanin. This compound may be called nitrogen dioxid hemocyanin. In the refrigerator, crystals of this substance remained stable for more than six months. Solutions of it, sealed in glass tubes, have remained stable for seven to twenty months. Nitrogen dioxid hemocyanin does not fix oxygen. The same chemical group present in hemocyanin may unite either with oxygen or with nitrogen dioxid. Hemocyanin does not form colored compounds with methane, ethylene or acetylene, at least above 36° C., the dissociation temperature. The authors worked with a temperature of 20° C., but experiments should be made at a temperature much lower than this.

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#### **A Method for the Quantitative Estimation of Minute Amounts of Gaseous Oxygen and Its Application to Respiratory Air.**

*Howard M. Sheaff, J. Biol. Chem., 52: 35, May, 1922.*

To determine whether nerve tissue used oxygen gas, and if so whether the consumption was increased during the passage of the excitatory stages, an apparatus was devised in which oxygen in the presence of nitric oxid was exposed to sodium hydroxid and the nitrite thus formed measured colorimetrically. Preliminary determinations indicated that the principle could be applied in these studies. The apparatus employed (illustrated) was connected at 4 different points with reservoirs containing 0.1 n. sodium hydroxid, nitric oxid, hydrogen, and respiration air, respectively. A microchemical method for the estimation of oxygen was devised depending upon the colorimetric estimation of nitrite formed in the interaction of oxygen and nitric



oxid in the presence of sodium hydroxid. In preparing samples of respiration air, the tissue used was the excised sciatic nerve of the frog, *Rana pipiens*. The excised nerve was placed at once in Ringer's solution, removed gently to dry on washed filter paper, weighed, and placed in a respiration chamber. Prepared respiration air was passed through the chamber for such a time as experience had shown sufficient to wash it completely of air previously contained. A nerve was considered as "resting" if prepared with sharp instruments, handled speedily, and placed gently on uncharged electrodes of the chamber; "stimulated" if prepared in the same way, but treated through electrodes with rapid induced shocks which were shown in the muscle-nerve preparation of the other leg of the frog to be just sufficient to cause response of the muscle when applied to the proximal end of the nerve, stimulation being continued through the period of respiration.

The author found that the microchemical method was sufficiently delicate for measuring amounts of oxygen of the order of magnitude  $1 \times 10^{-7}$  gm. or less than 0.1 c.mm. of the gas. Application of the method to the microrespiration of frogs' sciatic nerves showed that from 0.434 to  $0.76 \times 10^{-5}$  gm. oxygen is used by 10 mg. of nerve per 10 min. in the "resting" state and from 1.32 to  $1.51 \times 10^{-5}$  gm. when stimulated by weak induced shocks.

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#### **The Usefulness of the Colorimetric Method in the Determination of the Uric Acid Content of the Blood.**

*K. Harpuder and R. Mond, Ztschr. f. d. ges. exper. Med., 27:54. Berlin, March 25, 1922.*

The authors have tested the most useful modifications of the method of Folin and Denis. Studies of the methods of Steinitz, Maasse and Zondek and Neubauer and Bass showed great errors in all 3 of these methods. Determinations were made of the pure blood and of the same blood after weighed quantities of uric acid had been added. The amounts of recovered uric acid varied considerably in all 3 methods, being on the average 50, 44.2 and 41%. The causes of this probably are that the albumin coagulum absorbed uric acid, that dealbuminization was insufficient, that the solutions contained substances that give a blue color with phosphotungstic acid, and that too small quantities of blood were used. These conditions are manifested in the fact that, unlike in the blood filtrate, uric acid added to normosal solutions can be demonstrated quantitatively by the colorimetric method. That a considerable error is due to dealbuminization was shown in the following way: The well-washed albumin coagulum was hydrolyzed with 25% sulphuric acid, acidified with acetic acid and filtered. Copper oxid was added to the filtrate, the solution filtered and washed free of amino-acids. It was again filtered, sodium sulphite added to the filtrate, refiltered and washed. The filtrate was concentrated to 5 c.c. and the uric acid determined colorimetrically after the addition of phosphotungstic acid and 10 c.c. saturated sodium hydroxid solution. Therefore colorimetric determination from the blood gives only a rough approximation of the uric acid content and definite conclusions must not be drawn from it.

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**Uric Acid Estimation in Tissue Extracts.**

*H. Steudel and K. Suzuki, Hoppe-Seyler's Ztschr. f. physiol. Chem., 119: 166, Berlin, April 20, 1922.*

As minute amounts of uric acid may be estimated in urine and blood by Folin's method, this method, based on the reduction of phosphotungstic acid in alkaline solution to form blue compounds, was applied to organic extracts, the determination of the fate of the purin bodies in tissue extracts being attempted. The experiments were carried out with bovine spleen, which was comminuted in the meat-grinder, brought to the boiling point in water feebly acidified with acetic acid, and filtered hot. Extraction was repeated several times, the extracts precipitated in ammoniacal silver solution, hydrogen sulphid added to the precipitate and the filtrate concentrated under weak acid reaction. The residue was, however, easily soluble in water acidified with hydrochloric acid in contradistinction to uric acid, did not show the characteristic forms of uric acid but yielded Folin's uric acid reaction, responded positively to the Weidel test and in soda-alkaline solution, the diazo-reaction. Obviously one was dealing with a mixture of alloxur bases. The experiments accordingly showed that uric acid cannot be obtained from normal organs. Folin's method therefore is not applicable to tissue liquids without previous manipulation. Before its application uric acid must be isolated quantitatively by a preliminary experiment and its amount compared to that combined colorimetrically.

Folin's method can be employed only when the reduction of phosphotungstic acid is due actually to uric acid and not to any other substance. In spleen extracts ferments are present which may convert the primarily contained nuclein bases, guanin and adenin, into xanthin and hypoxanthin and finally into uric acid when the extracts are aërated. For that reason, when uric acid could not be detected in the preceding experiments fresh spleen extracts were employed.

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**Studies on Uric Acid. I. Examination of the Variables in the Folin and Wu Uric Acid Method.**

*George W. Pucher, J. Biol. Chem., 52: 317, May, 1922.*

Upon reviewing the literature relative to the quantitative estimation of uric acid in blood, Pucher found the average uric-acid recovery recorded to be only 80-85%. He considers Folin and Wu's recently announced method for the determination of uric acid to be the most rapid and accurate available for small quantities of blood. He presents experimental data to show that: (a) Within the accuracy of the Duboscq colorimeter (2 to 3%) the readings are proportional to the amount of uric acid present without applying any corrections. (b) Uric acid must be precipitated in neutral solution by silver lactate, and only under these conditions are consistent quantitative results obtained. (c) The precipitation of uric acid is very sensitive to mineral acid, but practically unaffected by lactic acid. (d) Temperatures below 26° C. have no effect on the solubility of silver urate. (e) Recovery by Folin and Wu's technic is consistently about 75%. (f) The loss must be due

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to mechanical retention or absorption by the precipitated proteins. (g) The use of trichloroacetic acid as the protein precipitant permits the recovery of only 50% of uric acid.

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**Studies on Uric Acid. II. A Modification of the Folin and Wu Uric Acid Method.**

*George W. Pucher, J. Biol. Chem., 52: 329, May, 1922.*

The author claims his modification (employing hot coagulation and filtration of the blood proteins) is more rapid and increases the uric acid yield to 93%. He has also combined 3 of Folin's reagents (the solutions of sodium sulphite, sodium cyanid and sodium carbonate) into 1 solution the concentration of which he adjusts so that the volume used (5 to 10 c.c.) contains the same proportions of each reagent as recommended by Folin. The reagents are: (1) uric acid standard prepared according to Folin; (2) protein precipitant prepared according to Folin; (3) dilute ammonia, 14 c.c. of concentrated ammonia diluted to 500 c.c.; (4) silver lactate reagent, 5% silver lactate in 5% lactic acid; (5) silver salt decomposition, a 10% solution of sodium chlorid in 0.1 n. hydrochloric acid. The combined reagent consisted of the following amounts of C. P. chemicals dissolved in warm water, made up to 1 liter, and filtered: sodium sulphite (anhydrous) 20 gm.; sodium carbonate (anhydrous) 120 gm.; sodium cyanid (100% NaCN basis) 5 gm.; (7) the uric acid reagent recommended by Folin and Denis.

Pucher's method is as follows: With a Folin pipette 5 c.c. of oxalated (excess oxalate *must* be avoided) whole blood are measured into a 125 c.c. long, narrow-necked Florence flask. The blood is laked with 35 c.c. of water and then 5 c.c. of sodium tungstate, followed by 5 c.c. of the 2/3 n. sulphuric acid are added. The flask is vigorously shaken and after standing about ten minutes (when the color must be a chocolate brown), immersed in a boiling water bath (from 95 to 98° C.) for five to eight minutes. After this period it is removed, shaken gently, and filtered immediately. To 20 c.c. of the filtrate (cooled to room temperature) in a 50 c.c. centrifuge tube are added 0.5 c.c. of the dilute ammonia and then with stirring 3 c.c. of the silver lactate reagent. After standing ten to fifteen minutes the solution is centrifuged for two minutes and the clear supernatant liquid carefully poured off. The residue is then thoroughly triturated with 2 c.c. of the 10% sodium chlorid in 0.1 n. hydrochloric acid, the stirring rod and sides of the tube washed with 10 c.c. of water and again centrifuged. The clear liquid is now poured into a 25 c.c. volumetric flask. Next pipette 1 c.c. of the standard uric acid into a 50 c.c. volumetric flask, washing down the sides with 4 c.c. of the 0.1 n. hydrochloric acid and 20 c.c. of water. Then add with shaking 10 c.c. of the combined reagent to the standard, and 5 c.c. to the unknown solution. Allow to stand for at least ten minutes; to the standard (50 c.c. volumetric flask) add 1 c.c. and to the unknown (25 c.c. volumetric flask) 0.5 c.c. of the uric acid reagent. Shake, let stand three to five minutes, dilute to the proper marks, and obtain the average of 6 to 10 readings made in the dark room. The calculation is as follows: Setting of standard (10 or 20 mm.)  $\times$  mg.

of uric acid in standard solution used for colorimetric comparison  $\times 50$  (usually 0.1 mg.)  $\div 2$  (reading of unknown) = mg. of uric acid per 100 c.c. of whole blood.

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**Simple and Practical Modification of the Ureometer of Danecy.**

*Gennaro Candido, Riforma med., 38:417, Naples, May 1, 1922.*

The writer has substituted for the upper stopcock of the ureometer of Danecy a simple tube of fusible glass, drawn in the flame, about 7 cm. long, with the inferior aperture of 7 mm. and the superior about 3 mm., which passes through the rubber stopper of the test-tube, adhering to it as closely as possible.

The reaction is carried out in the usual way. The reagents are introduced, and the upper aperture of the glass tube closed either with a rubber stopper or with the finger. The apparatus is turned upside down several times to produce proper mixture of the liquids and after several minutes, when the reaction is terminated, maintaining the apparatus upside down, the finger is removed or the gum stopper taken out. The tension of the gas permits escape of the liquid and results are obtained identical with the regular apparatus of Danecy.

The advantages of the proposed modification consist in a simplification of the maneuvers of performing the reaction, it not being necessary to open and close the stopcock, and especially in the possibility of substituting the glass tube with great facility, while in Danecy's apparatus, if it is necessary to repair the stopcock, one is obliged to send it to a factory. Whether the modification is definitely accepted or not, it merits consideration because of its simplicity and practicability and its aid in repairing the ureometer of Danecy, especially for those who are far removed from the center, where it is not always easy to procure a new apparatus.

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**An Accurate Ureometer for Determination of the Blood Urea.**

*R. Douris, Bull. d. sc. pharmacol., 29:238, Paris, May, 1922.*

Most of the methods in current use are inexact. Normal blood contains 0.30-0.50 gm. urea per liter. The volume of nitrogen in 5 or 10 c.c. blood is often only a fraction of a cubic centimeter. If the collection tube is too small, the gas may form bubbles or uneven capillary action may prevent a level reading surface. The author has devised an apparatus permitting the reading of a gaseous volume of less than 0.005 c.c. A long and fine U-tube is filled with a colored liquid, which is displaced by a gas liberated by the action of sodium hypobromite on the specimen of blood. The blood is introduced by a tube fitted with a glass cock, the hypobromite being added by a bulb or ampule, attached to the side of the reservoir. The cleared blood is introduced and neutralized with 2 drops dilute soda solution, as indicated by alcoholic solution phenolphthalein. Action of the hypobromite produces a difference of level in the arms of the U-tube. The apparatus is left until the 2 levels are constant. The solution is then drawn off until the levels in the arms correspond, and the displacement

is read on a scale. As 2 c.c. in the reading arm of the U-tube occupies a length of about 40 cm., 0.005 c.c. may be easily read. In order to avoid corrections for temperature and pressure, the reading is also obtained for 1 c.c. of a 1:500 solution urea. The final reading, X, is equivalent to the quotient obtained by dividing the product of 0.80 times N by n, N being the reading obtained by treating 5 c.c. of the cleared liquid corresponding to 2.5 c.c. blood, and n being the reading obtained by treating the urea solution. X represents the quantity of urea per liter blood. This apparatus is simple, rapid, and may easily be cleaned. A drawing illustrates its action.

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**Estimation of Urea Decomposed by Urease in the Carbon Dioxid Component of the Conversion Product.**

*Zoltán Aszodi, Biochem. Ztschr., 128: 391, Berlin, March 28, 1922.*

Estimation of urea, after its conversion by urease, from the carbon dioxid component of the conversion product  $(\text{NH}_4)_2\text{CO}_3$ , is of great practical importance, and is effected easily with 2 apparatus. In one, urea is converted into  $(\text{NH}_4)_2\text{CO}_3$ , and carbon dioxid is then liberated; in the other, the amount of preformed carbon dioxid is determined by allowing the sulphuric acid to flow downward, without addition of urease and without placing the apparatus in the thermostat. By subtracting the second level from the first, and multiplying the remainder by the caliber of the apparatus, the level corresponding to the carbon dioxid liberated from only the converted urea is obtained in milligrams per cubic centimeter of urine employed. Presence of albumin or sugar does not interfere with the reaction.

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**A New Rapid Micromethod for Nitrogen Determination.**

*Acel Dezső, Orvosi hetil., 66: 194, Budapest, May 21, 1922.*

In this method the following supplies are necessary: (1) Uniform test-tubes made of Jena glass 20 mm. in diameter and 180 mm. long. (2) A so-called 3 c.c. microburet, accurately divided into hundredths. (3) A 1 c.c. pipet, accurately graduated by hundredths. (4) Concentrated  $\text{H}_2\text{SO}_4$  free of ammonia. (5) NaOH solution, 50 c.c. NaOH plus 100 c.c. water. (6) Nessler's reagent. The fresh reagent cannot be used; it is allowed to stand and the pure reagent poured off from the sediment; the reagent has a specific gravity of 1.28, is pale yellow and very corrosive. (7) A suitable salt solution, 50 gm. Rochelle salts in 100 c.c. warm distilled water. To avoid hyphomycetes 5 c.c. pure Nessler reagent is added to the solution. The two latter solutions should be kept in brown glasses with a paraffined cork. (8) Ammonium chlorid solution containing 0.02 mg. nitrogen to each cubic centimeter. It is well to use pure ammonium chlorid, otherwise the nitrogen content must be determined by Kjeldahl's method.

In the process of determination a measured quantity of the substance is put in the test-tube and 0.05 c.c.  $\text{H}_2\text{SO}_4$  is added. The same amount of  $\text{H}_2\text{SO}_4$  is put in another tube of the same kind without the



addition of the test substance, to serve as a control. Both tubes are heated over a small flame; after evaporation of the water the fluid becomes brown, but further heating again decolorizes it. The decomposition requires 4-5 minutes, after which 10 c.c. of ammonia-free distilled or tap water is added. Then are added in order 0.3 c.c. NaOH solution, 0.5 c.c. Rochelle salt solution, and finally, drop by drop, 0.5 c.c. of the Nessler reagent. After the latter solution becomes yellow or brown, depending on the ammonia content. The fluid in the control tube, if everything was free of ammonia, is yellow, as a result of coloring by the Nessler reagent. The amount of ammonia is determined by filling the microburet with ammonium chlorid solution and dropping ammonium chlorid into the colorless or yellow control tube until its color is identical with that in the other tube. The amount of ammonium chlorid used shows the amount of ammonia or nitrogen in the test substance. Colorimetry is carried out by placing the test-tubes against a white background in a well-lighted place and looking through them from one side. With some practice the finest shades of difference can be distinguished. The optimal zone for the determination of the nitrogen content lies between 0.004 and 0.03 mg. The method is of value in the examination of serum, residual nitrogen in serum and in urinary nitrogen determination.

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**The Differential Precipitation of the Proteins of Colostrum and a Method for the Determination of the Proteins in Colostrum.**

*Paul E. Howe, J. Biol. Chem., 52: 51, May, 1922.*

In this work, the general technic involved the direct determination of casein and the estimation of the remaining proteins by means of definite concentrations of a salt or by the use of different salts. A series of precipitations with anhydrous sodium sulphate was made and the casein precipitated from the filtrates of such precipitations. Tabulated data are presented which show that there are consecutive concentrations of sodium sulphate which, when added to diluted colostrum or milk, do not cause a marked increase in the quantity of protein precipitated and define a critical zone, on either side of which a small variation in the quantity of sodium sulphate added results in a relatively large difference in the quantity of protein precipitated. Critical zones were found to be at 14.0 to 14.2, 18.0 to 18.4, and 21 to 22% of sodium sulphate. Similar zones were obtained in the neutralized filtrates of colostrum from which the casein had been removed with acetic acid. Casein is not precipitated by 14.0 to 14.2% of sodium sulphate but is precipitated by 18.0 to 18.4% of sodium sulphate; it is also precipitated by acidification of the diluted colostrum with acetic acid or alum or by the acidification of the filtrate from a precipitation with sodium sulphate. If the sodium sulphate precipitation be made at a concentration less than 14.5%, the casein can be recovered completely by subsequent acidification of the filtrate. As a result of these observations, it is suggested that there exists a basis for the quantitative determination of the various proteins of colostrum or milk. The material separated at the various concentrations of sodium sulphate, when added to colostrum in the proportion of 31:1 is held to consist



of the following proteins or mixtures of proteins: (a) at 14.0 to 14.2% of sodium sulphate — of euglobulin; (b) at 18.0 to 18.4% of sodium sulphate — of euglobulin, pseudoglobulin I, and casein; and (c) at 21 to 22% of sodium sulphate — of euglobulin, pseudoglobulin I and II, and casein. With the values for casein and nonprotein nitrogen determined independently, one can calculate the quantities of the various proteins present in colostrum.

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**Is Albumin Coagulation by Heat Due to Hydrolysis.**

*Margit Hirsch-Pogany, Biochem. Ztschr., 128:396, Berlin, March 28, 1922.*

Nothing is known regarding the change taking place in albumin in heat-coagulation, but as complete coagulation occurs only in a weak acid solution it is possible that the entry of water into the albumin molecule is involved, as in acid hydrolysis. The experiments were conducted with egg albumin. Estimation of dried residue, of nitrogen by Kjeldahl's method, elementary analysis and ash determination were carried out on coagulable and noncoagulable parts. The experiments show that no alteration worth mentioning took place in content of dried residue. The other estimations also indicate that if hydrolysis is concerned at all in albumin coagulation it is so insignificant as to make its detection impossible.

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**The Action of Ultraviolet Light on Egg-Albumin in Relation to the Iso-Electric Point.**

*Janet H. Clark, Am. J. Physiol., 61:72, June 1, 1922.*

It is assumed that the physiologic action of light is due to the formation of photochemical compounds, and the formation of these compounds is due to the photo-electric action of light which, by producing an ionized condition in light-sensitive molecules, leads to subsequent chemical reactions. The photodynamic sensitization of substances, so that they react toward visible light, in the presence of certain dyes, in the same way that the untreated substance acts toward ultraviolet light, is thus explained. In the presence of a sensitizer the photo-electric threshold of the light-sensitive substance is shifted toward longer wave-lengths, so that it is photo-electric at these wave-lengths and is therefore ionized, with resultant chemical action, by visible light. To make this theory tenable it must be proved: (1) That the effect of ultraviolet light is due to the emission of electrons from light-sensitive atoms and molecules; and (2) that this emission takes place in visible, as well as in ultraviolet, light on the addition of a sensitizer. The second part of the proof is still wanting, but the results of the coagulation of egg-albumin by ultraviolet light, furnishes excellent evidence for the first part. In the experimental procedure, the white of a fresh egg was diluted to twice its volume with distilled water. The globulins were precipitated by half saturation with ammonium sulphate and removed by centrifuging and filtering. The albumin solution.

was then dialyzed for 2 days against distilled water which was frequently changed. The solution thus obtained was found to have a pH of 6.2. By means of indicators, solutions were prepared with pH ranging from 4.0 to 8.2. They were exposed to the quartz mercury arc, in quartz and glass test-tubes, for a succession of 15 minute periods, at a distance of 5 in. The temperature of the solutions did not rise above 32° C. during the exposure. No effect was found at any pH when a solution was exposed in a glass test-tube to the quartz mercury arc. Radiation through quartz, however, of a solution having a pH of 5.6 caused a precipitate to settle out which is not globulin but coagulated albumin, for it does not dissolve in 1% sodium chlorid nor in concentrated hydrochloric acid. The albumin is changed by radiation and becomes positively charged albumin, after which it is precipitated like globulin by half saturation with ammonium sulphate. Due to the photo-electric action of ultraviolet light on egg-albumin, radiation produces a state of greater aggregation when the albumin particles are negatively charged and a state of greater dispersion when they are uncharged or charged positively.

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#### **The Colloidal Behavior of Edestin.**

. *David I. Hitchcock, J. Gen. Physiol., 4: 597, May 20, 1922.*

Loeb has shown that the physical, chemical, and so-called colloidal properties of solutions of the proteins, gelatin, egg-albumin, and casein, can be simply explained by 2 general principles: (1) proteins are amphoteric electrolytes, reacting stoichiometrically with acids and bases to form salts capable of electrolytic dissociation; (2) the principle of Donnan's membrane equilibrium which is set up when 2 solutions are separated by a membrane impermeable to 1 ion of 1 of the solutions. This investigation was undertaken with the object of finding out whether these laws would explain the behavior of solutions of a protein of a different class, namely a globulin. The globulin selected for the purpose was edestin, prepared from ground hemp-seed by a modification of the Osborne method. Titration curves of solutions of edestin in acids and bases were obtained in the region where 0.45 gm. could be almost completely dissolved in 100 c.c.; i. e. below pH 5.0 and above pH 9.0. Solutions were prepared containing different quantities of acid or alkali of the same concentration with respect to edestin, and the pH values were ascertained by means of the hydrogen electrode, using a salt bridge of saturated potassium chlorid and a saturated potassium chlorid-calomel cell. The measurements were made at  $33^{\circ} \pm 0.5^{\circ}$ , and were referred to 0.1 n. HCl as a standard, its pH being taken as 1.036. Such titration experiments showed that the globulin edestin behaves like an amphoteric electrolyte, reacting stoichiometrically with acids and bases. Loeb has shown that when a solution of gelatin or egg-albumin in dilute acid is separated by a collodion membrane from an aqueous solution of the same acid, containing no protein, a difference in electrical potential exists between the 2 solutions. He found it possible accurately to calculate the magnitude of the potential difference with considerable accuracy from the pH of the 2 solutions on the basis of Donnan's theory. Experiments were carried out to determine

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whether similar results could be obtained with edestin. The potential difference developed between a solution of edestin chlorid or acetate separated by a collodion membrane from an acid solution free from protein was found to be influenced by salt concentration and pH in the way predicted by Donnan's theory of membrane equilibrium. The osmotic pressure of such edestin-acid salt solutions was found to be influenced by salt concentration and by pH in the same way as is the potential difference. Hitchcock concludes that the colloidal behavior of edestin is thus completely analogous to that observed by Loeb with gelatin, casein, and egg-albumin, and may be explained by Loeb's theory of colloidal behavior, which is based on the idea that proteins react stoichiometrically as amphoteric electrolytes, and on Donnan's theory of membrane equilibrium.

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**Simpler and More Practical Method for Determining the Presence of Indican in Urine.**

*V. Sebastiani, Policlinico (Pract. Sect.), 29:653, Rome, May 15, 1922.*

For purposes of demonstrating the presence of indican in the urine the author advises the use of commercial hydrochloric acid, to which is added a given quantity (not less than 2 gm. per thousand, and often more) of powdered rust or iron filings. In the latter case it is advisable to wait several days before using the reagent, to make sure that the ferrous chlorid formed at first has all been transformed into ferric chlorid.

When the reagent has been properly prepared, there is placed in a test tube enough urine to fill it to about one-third (occasionally previously dealbuminized), and enough of the crude hydrochloric acid prepared as above is added to fill the test-tube to about two-thirds; the mixture is allowed to stand for five to ten minutes; then about 2-3 c.c. chloroform are introduced, and the mixture is agitated thoroughly until all the indigotin has been extracted. On allowing the test-tube to stand there will be a sedimentation of the chloroform; the supernatant fluid is decanted, water being added in its stead, and the mixture thus formed again agitated for some time. This washing separates the chloroform from the ferric chlorid, and the former appears — if the reaction is positive — colored a more or less intense blue, occasionally a violaceous hue.

The modification here proposed, in addition to its noninterference with the sensitiveness of the reaction, has the advantage over the original method of placing within reach of the practitioner a reagent of much more modest cost than pure hydrochloric acid, one which may be readily found almost anywhere, and which may be easily prepared on the spot so as to enhance its oxidizing properties.

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**Piperazin and Lycetol. Two New Reactions.**

*Juan A. Sanchez, Semana méd., 29:700, Buenos Aires, May 4, 1922.*

Piperazin is a secondary heterocyclic base (diethylenediamin),  
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occurs in colorless rhomboid crystals (obtained by the use of alcohol), fuses at  $104^{\circ}$  C. and boils at  $146^{\circ}$  C. It is readily soluble in water, and is hygroscopic; its hydrate crystallizes with 6 molecules of water, and has a boiling point of  $130^{\circ}$  C. The chemical reaction is strongly alkaline, forming salts with acids: (1) urate,  $C_4H_{10}N_2 \cdot C_5H_4O_3N_4$ ; which is of therapeutic value as a solvent of uric acid; (2) chloroplatinate,  $C_4H_{10}N_2 \cdot 2ClH \cdot HCl_4$ , in yellow needles, slightly soluble in alcohol; (3) picrate,  $C_4H_{10}N_2 (C_6H_2[NO_2]_3OH)$  in yellow needles, insoluble in alcohol; and (4) hydrochlorate,  $C_4H_{10}N_2 \cdot 2Cl H + H_2O$ , insoluble in alcohol and soluble in water. Iodobismuth acid, in dilute solutions of piperazin, slightly acidulated with HCl, forms a microcrystalline, scarlet precipitate, resembling iodid of mercury. Mercurous chlorid forms an abundant white precipitate in 1% solutions of piperazin. Nessler's reagent forms a white precipitate.

Two new reactions of piperazin are described: (1) Nitrification reaction: When sodium nitrate is added to piperazin in an acid medium, and agitated, a white precipitate is obtained which is readily soluble in water. This product, filtered and washed, may be dissolved in chloroform. The residue, with the addition of phenol and sulphuric acid, forms a product which, when alkalinized, gives an intense indigo blue stain. This stain is used in the Liebermann reaction. (2) Oxidation reaction: When piperazin is oxidized with potassium permanganate in a sulphuric medium, and the product distilled, formaldehyd is found. The liquid residue in the distillation apparatus, alkalinized and heated, gives out abundant ammoniac fumes resulting from the dissociation of piperazin.

Lycetol is the tartrate of 2.5 alpha-dimethylpiperazin, which crystallizes with 3 molecules of water, having a melting point of  $240^{\circ}$  C. and decomposing at this temperature. It is a white, microcrystalline substance, easily soluble in water. It has, in general, the same reactions as piperazin, except that mercurous chlorid does not form a precipitate with lycetol. Lead acetate gives a white precipitate which dissolves in ammonia and in nitric acid. The reactions correspond to those of piperazin. When it is dissolved with sodium nitrate in an acid medium, and shaken, a white substance is precipitated which is only slightly water-soluble but is soluble in chloroform, as is the case with piperazin. This substance is paradinitrosodimethyl 2,5 piperazin; its melting point is  $172^{\circ}$  C. The oxidation reaction corresponds to that of piperazin.

Bayer's reaction: If 0.1 gm. lycetol is dissolved in 1 c.c. water, acidulated with one drop acetic acid, and 10 drops potassium acetate (20%) and 5 c.c. alcohol are added, and the mixture shaken, a crystalline precipitate of acid potassium tartrate is formed. Berg's reaction: If to 50 c.c. water one adds 1 drop iron chlorid solution, and 2 drops HCl, the resulting liquid is colorless. If 0.05 gm. lycetol, diluted in 5 c.c. water, is added, a yellow coloration appears, demonstrating the alcoholic functions of tartaric acid. Mohler-Denigé's reaction: The reagent consists of 2% aqueous solution resorcin, and 0.5 c.c.  $H_2SO_4$ . To 0.02 gm. lycetol is added 2 c.c. concentrated  $H_2SO_4$ , and 2-4 drops of the reagent; this is heated to  $130^{\circ}$ - $140^{\circ}$  C. A violet red color appears, due to the resorcin condensation of the tartaric acid of lycetol.

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**Tyramin (P-Oxyphenylethylamin) as the Active Principle of the Drug Semina Cardui Mariae (Prickly Thistle Seeds).**

*Alfred Ullmann, Biochem. Ztschr., 128:402, Berlin, March 28, 1922.*

The physiologic efficacy of extracts from Semina cardui Mariae was investigated by Boruttau who found the same increase of blood pressure as with ergot of rye. In order to isolate the active principle, p-oxyphenylethylamin, 1 kg. of the ground drug was extracted four days with water, lead acetate added, and the whole filtered; the filtrate concentrated in vacuo and acidified with sulphuric acid, when a precipitate formed which was removed by filtration. To this filtrate phosphotungstic acid was added, the precipitate separated from the liquid and washed in 5% sulphuric acid. The precipitate was then suspended in water, barium hydroxid was added, the insoluble barium compounds filtered off, excess barium hydroxid precipitated with carbonic acid, filtered, neutralized with hydrochloric acid and concentrated in vacuo. The solution so obtained raised blood pressure markedly, depressed respiration, increased the heart-beat, and these symptoms followed the typical course observed after injection of tyramin. The solution was rendered alkaline with soda solution and the base obtained by agitation with amyl alcohol. The base was benzoylated according to Schotten-Baumann's method and the benzoyl derivative allowed to crystallize from alcohol. The melting point was 169° C. The same result was yielded by a salt having a mixed melting point, prepared from anisic aldehyd. The experiments show p-oxyphenylethylamin to be the physiologically active principle of Semina cardui Mariae. The pharmacologic action of the vegetable uterine and styptic remedies is the same as that of Capsella Bursae pastoris and ergot of rye and they probably contain, besides tyramin, histamin and amylamin, acetylcholin bodies of unknown composition that are activated only by the ferments.

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**A Method of Quantitative Determination of Trypsin. A Modification of Gross' Method.**

*Sotaro Kai, J. Biol. Chem., 52:133, May, 1922.*

Following Gross' procedure for the quantitative determination of trypsin, 10 c.c. of an alkaline casein solution, which has been prepared by dissolving 1 gm. of dry casein and 1 gm. of sodium carbonate in 1000 c.c. of distilled water, are introduced into each of a series of test-tubes. To each increasing quantities of trypsin are added, and the tubes are incubated in a thermostat kept at 40° C. After 15 minutes of digestion, a few drops of 10% acetic acid are added to each tube. A turbidity will be produced in those tubes in which digestion is incomplete. The concentration is then calculated from the smallest quantity of the trypsin solution which does not produce the turbidity. In a method which Kai believes is still more simple than that of Gross the necessary reagents are: (1) Alkaline casein solution prepared by dissolving 0.1 gm. of pure casein in 15 c.c. of 0.1 n. NaOH. Add 400 c.c. distilled water and titrate 10 c.c. of this solution until just colorless (Sec. 1—Page 80)



to phenolphthalein, using 0.01 n. HCl. Add a corresponding amount of the acid to the remainder and make up to 500 c.c. (0.2% casein solution). (2) Mixture of sodium hydroxid and acetic acid: 100 c.c. of this solution contain 17.2 c.c. of normal soda and 33.7 c.c. of normal acetic acid. (3) Standard trypsin solution, prepared by dissolving 0.01 gm. of good commercial trypsin in 10 c.c. of water; filter it off and add toluene. The procedure is as follows: Transfer 25 c.c. of the stock alkaline casein solution to each of two 50 c.c. flasks. Warm to 40° C. in the thermostat. To one of these add 1 c.c. of the standard trypsin solution, and to the other, 1 c.c. of the unknown, noting the time of this addition. Mix well and replace in the thermostat. At intervals of 5 to 10 minutes, 2 c.c. of the digesting mixture are pipetted off from each flask, and mixed with 1 c.c. of sodium-hydroxid acetic acid mixture in a test-tube. The time at which the digest fails to give any white precipitate is noted. The standard under this condition will usually require about 15 to 20 minutes. If the unknown requires twice as long as the standard, its concentration is one-half of the concentration of the standard. The author presents 2 tables which show (1) that the rate of digestion is simply proportional to the amount of trypsin and the time of the digestion is, therefore, inversely proportional to the concentration of the trypsin, i. e. the time of concentration of enzyme multiplied by the time of digestion is a constant; (2) that the rate of digestion is inversely proportional to the amount of casein, and the time of digestion is, therefore, directly proportional to the concentration of the casein, i. e. the time of digestion divided by the concentration of casein is constant.

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#### Protein Enzymes.

*Rudolf Ehrenberg, Biochem. Ztschr., 128:431, Berlin, March 28, 1922.*

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The enzymes are regarded as catalyzers, which presupposes that the respective reaction proceeds as such, though immeasurably slowly, and that the enzyme interferes in a process as a contact substance. Doubts are felt regarding this, however, because the prevailing theory of enzymes shows no connection between the two chief characteristics, namely, enzymatic action and thermolability. This view is supported by a comparison of pepsin on the one hand and of trypsin on the other. At a higher temperature the former is inactivated much more rapidly than the latter and the digestive action of pepsin at lower temperatures is correspondingly much greater than that of trypsin. If the process of activation is a disintegrating one and the enzyme particles become smaller their capacity for dialysis through membranes might be expected to increase so that active dialysates of warmed enzyme solutions would be much smaller. Actually both pepsin and trypsin dialyse better in the activated condition. The protection afforded by the substrate against inactivation by heat is supposed to depend on the combination of the ferment with the substrate particles, whereby dispersive effects would be attained. The experiments show that only a certain portion of the total amounts of active ferments traverse the filter, that this portion is increased by previous warming and that it increases still further.



with addition of substrate during warming. The assumption of a regeneration or new formation from the substrate has gained in probability by these researches and it is possible that the degenerated or subsequently formed ferment differs according to the origin of the substrate. As a matter of fact the experiments show that the more diverse the substrates (liver, kidney, testicle, tubercle were tried) the greater is the relative specificity. Thus, carcinoma ferment digested carcinoma extract much better than liver ferment although the former was accidentally diluted 100% more than the latter. The first part of the enzymatic process consists in disintegration as appears from dialysing and filtering experiments. Whether the further course of the process up to the irreversible end-conditions remains a disintegrating one cannot be determined from the hitherto conducted researches. In the dialytic cultivation experiments a clouding appeared in the external liquid of the parchment dialyzer after more than twenty-four hours and sometimes a skin formed which behaved similarly to coagulated albumin. It dissolves in strong hydrochloric acid, gives a red coloration with Millon's reagent, dissolves in peptohydrochloric acid, but is unaltered by pepsin. On the addition of glycerin to the external liquid, however, neither dissolved nor undissolved albumin ever appeared therein. When derived from casein the skin arrested the digestion of casein. The dialysis of casein dissolved in phosphates against the same salt solution for forty-eight hours produced no acid clouding in either solution and yielded no albumin test whatever but the solutions possessed a fermentative action toward casein. The enzyme activity thus produced was thermolabile. The experiments have not decided the question of how this active substance acts in the protein molecule. Pepsin is said to effect this through tyrosin. The polymerizing tendencies of phenol derivatives would also belong to this category. On the whole the enzymatic process is to be regarded as a total reaction from the standpoint of the theory of chemical equilibrium. A whole chain of reactions exists in the case of substances that undoubtedly belong to the entire group of albuminous bodies in which, however, initial disintegration processes, whether of a chemical or colloidal nature, and later synthetic processes are involved, apparently requiring the participation of energy-yielding processes which consist in oxidations, perhaps also in fermentations, and possibly sugar fermentations. As appears from the occurrence of the skins, the autosynthesis of enzymes also acts synthetically on the substrate's cleavage products and produces larger total aggregates.

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#### **The Origin of Amylase and Maltase in Plants.**

*W. Palladin and Helene Popoff, Biochem. Ztschr., 128: 487, Berlin, March 28, 1922.*

Amylase and maltase occur frequently in cellular juice. Higher plants always contain both ferments as diastase. The effect of their fermentative action was deduced from the disappearance of starch and the appearance of sugar that reduces Fehling's solution. Brown and Morris showed that diastase is produced in germinating barley at the expense of protoplasm and cell nucleus, and is then eliminated. Such

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diastase is termed a secretion diastase and is found in germinating seeds. Much more widely distributed is the translocation diastase, which is found in all leaves and other vegetative organs. In a former research it was found that peroxidase in plants is not confined exclusively to cell juice but is largely associated with protoplasts. During autolysis this peroxidase goes into solution, i. e. it is a product of protoplasmic disintegration. It was desired to determine, therefore, whether diastase also occurs in plants in combination with protoplasts and whether it is likewise split from protoplasts during autolysis. For this purpose all of the dissolved diastase was removed from the leaves by comminuting the latter carefully, diluting with water and subjecting the mass to prolonged autolysis in the presence of chloroform. After this treatment only the diastase combined with protoplasts was left. Soluble starch was then added, the functioning of diastase deduced from the disappearance of the reaction to iodine and the quantity of sugar estimated with Fehling's solution. The experimental temperature was 25-32° C. The experiments showed that diastase combined with protoplasts is split off during autolysis and goes into solution.

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**O-Emulsin (Oxynitrilese), D-Emulsin (Oxynitrilase), Carboligases.**

*L. Rosenthaler, Biochem. Ztschr., 128:606, Berlin, March 28, 1922.*

In reference to the communication by Nordefeldt ("The importance of acidity in the synthesis of oxynitril and the nonexistence of Rosenthaler's synemulsin," *Biochem. Ztschr., 118:15, 1921*) Rosenthaler states that the designation synemulsin applies only to that constituent of emulsin which produces the asymmetric structure of nitril synthesis. Further, he shows that those components of emulsin which accelerate hydrocyanic acid addition are chiefly of a nonenzymatic nature and, therefore, not identical with the synemulsin oxynitrilese. Neuberg, Hirsch and Liebermann stated in the *Biochem. Ztschr., 115:282, 1921, and 121:311, 1921*, that in the fermentation of sugar or pyroracemic acid, benzaldehyd yields the ketone alcohol  $C_6H_5CHOHCOCH_3$ , and claimed that this enzyme, a so-called carboligase, is the first to link carbons. In reply the following is stated: (1) The compounds of aldehyds with halogen hydracid, hydrogen ferricyanid and hydrogen cobalticyanid are generally regarded as oxonium combinations, in accordance with Von Bayer's and Villiger's views and are, therefore, not comparable with oxynitrils. (2) Oxynitrils may be saponified to form acids and no one has maintained in regard to these that the combination of the C of the carboxyl group is essentially different from that of the C of the CN group from which the latter is derived. (3) Dissociation with dissolution of a C-C bond is not restricted to oxynitrils. One need only remember the conversion of hexaphenyl ethane into triphenyl methyl, in spite of which hexaphenyl ethane has never been designated as an addition combination. From this it appears that addition of hydrocyanic acid to aldehyds represents a true linkage of 2 carbon atoms and that the enzymatic formation of optically active oxynitrils is the first known instance of a carboligase action.

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**Classification of Carboligase.**

*C. Neuberg and J. Hirsch, Biochem. Ztschr., 128:608, Berlin, March 28, 1922.*

The following facts are adduced regarding the nomenclature of oxynitrilese and carboligase. Rosenthaler's oxynitrilese, contained in emulsin, is not a synthetizing ferment. It induces, essentially, the optical activity of the cyanhydrin which is formed by the automatic union of the constituents and which is hydrolyzable by emulsin as well as chemically. So far as can be judged, carboligase represents a synthetizing enzyme, which effects the linkage of those carbon chains which do not unite spontaneously and are not cleaved by fermentation or chemical hydrolysis.

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**Carboligase. IV. Biosynthetic Carbon Chain Linkage during Fermentation.**

*Carl Neuberg and Heinz Ohle, Biochem. Ztschr., 128:610, Berlin, March 28, 1922.*

Hitherto it has been considered that the carboligatic union of bitter almond oil and residual acetaldehyd, during fermentation of sugar or pyroracemic acid, produced a carbon chain having the structure  $C_6H_5CHOHCOCH_3$  of phenyl pyroracemic alcohol. For the biosynthesis of this l-phenyl acetyl carbinol, 1.25 kg. starch syrup was dissolved in 25 liters water with 1 kg. yeast. After  $\frac{1}{2}$  hour initial fermentation, 100 gm. benzaldehyd were added gradually. Three days later the yeast was filtered through diatomaceous earth, the filtrate impregnated with ether, the ethereal extract dried with sodium sulphate, filtered, and the ether evaporated. The residue, weighing 91 gm., was dissolved in ether, and soda solution was added to remove acids. The liquid was then shaken with about 200 c.c. sodium bisulphite solution. The residual ethereal solution contained only the benzyl alcohol fraction. The soda alkalized solution (acid fraction) was acidified with dilute sulphuric acid, which caused separation of crystalline plates that were filtered off and recrystallized from benzin. Melting point was  $121^\circ C.$ , identifying the substance as benzoic acid. After evaporation of the ethereal solution that was dried with sodium sulphate the residue was distilled in vacuo and proved to be benzyl alcohol. The sodium bisulphite solution was treated with sodium bicarbonate, extracted with ether, the ether evaporated off, and then distilled in vacuo, whereupon the addition of thiosemicarbazid yielded optically inactive thiosemicarbazon. The semicarbazon of l-phenyl acetyl carbinol  $C_6H_5CHOH.C(:N.NH.CO.NH_2).CH_3$  has a melting point of  $194^\circ C.$  The thiosemicarbazon of l-phenyl acetyl carbinol  $C_6H_5CHOH.C(:C.NH.CS.-NH_2).CH_3$  was obtained from 1 gm. indol by pouring over the latter a hot solution of 0.6 gm. thiosemicarbazid in 10 gm. pyridin. The product has a melting point of  $207^\circ C.$  and was optically active. Attempts to determine the indol titrimetrically by utilizing its considerable reducing power toward Fehling's solution gave somewhat diverse values according to whether the estimation was carried out slowly or rapidly. Also, the estimation of the ketone alcohol as p-nitrophyl osazone yielded unsatisfactory results. Only the isolation of the indol gave useful

results. Of biosynthetic by-products the following may be mentioned: Dioxypropyl benzol (acetyl benzoyl)  $C_6H_5.CO.CO.CH_3$ . The phenyl hydrazone has a melting point of  $145-146^\circ C$ . Another by-product of biosynthesis was the benzyl alcohol benzyl ester of alpha-naphthylcarbaminoic acid,  $C_6H_5.CH_2.OCO.NH.C_{10}H_7$ , melting point  $133.5^\circ C$ ., which was obtained by mixing equimolecular amounts of benzyl alcohol and alpha-naphthyl isocyanate. The carbolic origin of ketone alcohol, upon the addition of an aldehyd to a fermenting sugar solution, touches closely the problem of phytochemic reduction. The phytochemic reduction of aldehyds does not proceed according to the scheme of the dismutation reaction, but the oxidation process corresponds to the reduction process. The primary oxidation equivalent is obviously provided by the acetaldehyd.

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**The Temperature Coefficient in Starch Cleavage and the Thermostability of Maltase and Ptyalin.**

*Efr. Ernstrom, Hoppe-Seyler's Ztschr. f. physiol. Chem., 119:190, Berlin, April 20, 1922.*

Experiments were conducted on the influence of temperature on certain amylolytic enzymes and particularly on the conditions for the action of maltase and ptyalin. The optimum reaction of maltase in an acetate mixture at  $37^\circ C$ . was found at pH 5. The optimal zone lies between pH 4 and 6. The action of the ptyalin in a phosphate mixture at  $37^\circ$  showed optimum pH 6.5. As not merely H and OH ions but also others, especially chlorin ion, play a great part in enzymatic processes, the action of sodium chlorid was investigated in this respect. It was found that the action of amylase does not depend on sodium chlorid in weak concentration. In a 0.026N sodium chlorid solution the action begins to diminish slightly and diminishes more and more with increasing sodium chlorid concentration. Without chlorid ptyalin is entirely inactive. The maximum ptyalin action is obtained with 0.017 normal sodium chlorid. The optimum lies between 1 and 1.6% and agrees with the physiologic sodium chlorid content of the saliva.

It is known that the action of amylases increases up to an optimum with rising temperature and then diminishes rapidly. In the experiments maltase and ptyalin retained a part of their activity even at  $0^\circ C$ . The temperature coefficient values fall with increasing temperature both for maltase and ptyalin; between  $10^\circ$  and  $30^\circ$  it is fairly constant.

The experiments employed amylase prepared from germinated barley, 300 gm. of which were mixed with sea-sand, well softened and allowed to stand two days, filtered and dialyzed by Störensens's method. Enzyme solutions employed gave dried residues of 0.63, 0.75, 0.56, 0.86, 0.82, 0.68 and 0.94 mg. per cubic centimeter. Saliva was collected after disinfection of the oral cavity, filtered, kaolin added and dialyzed against distilled water, then filtered and a few drops toluol added. The dried residues were: 1.1, 0.85, 1.2, 0.76, 0.94, 0.91 and 0.87 mg. per cubic centimeter. Two percent starch solutions were used. The experiments were carried out in Erlenmeyer flasks kept at constant temperature on a water bath. With pipets 50 c.c. 2% starch solution, 20 c.c. buffer mixture (0.29 normal phosphate solution,) the enzyme solution and water were introduced into the flasks so that the reaction

mixture always consisted of 100 c.c. The enzyme, previously warmed on the water bath, was added only after the starch-buffer mixture had attained constant temperature. After varying periods 10 c.c. liquid were removed from the samples and pipetted in to a Fehling solution. The sugar obtained estimated by Bertrand's method as maltase and the reaction constant calculated in accordance with the formula  $k=1 \div t \log a \div (a-x)$ ;  $a$  was taken to equal 70 and  $x$  the sugar formed during the reaction. The warming of the enzyme-phosphate mixture always took place in sealed tubes. The tubes were well steamed before use.

For ptyalin the amount of sodium chlorid was determined with which constant  $A$  is greatest in the region  $30-40^\circ$ , and found to be about 100 gm. sodium chlorid in 100 c.c. reaction mixture and the ptyalin action was also greatest with this. The constant  $A$  is not related in any way to the acidity. Maltase partly inactivated by heat does not become reactivated. As buffer in phosphate mixture maltase is most stable at pH 5.9, namely, in a slightly more alkaline solution than that corresponding to the maximum action. No change in stability was observable when maltase solution was warmed in the presence of 0.09N sodium chlorid solution. Ptyalin can be stabilized as buffer in the phosphate mixture where pH=6.0-6.1, i. e. in a slightly more acid solution than corresponds to the maximum action (6.4-6.5). The solution's sodium chlorid content exerts a strong influence on the stability of ptyalin, stability being greatest in 0.1N sodium chlorid solution. Sodium chlorid does not augment the stability of maltose. At  $54-56^\circ$  the latter's stability diminishes, when heated one hour, to half its activity at  $37^\circ$ . Ptyalin is destroyed at about  $56.5^\circ$  with optimal pH and 0.01 N sodium chlorid solution. In the presence of an optimal amount of sodium chlorid and with optimal acidity, the temperature at which ptyalin is destroyed lies at about  $57.5^\circ$  and without sodium chlorid at about  $51.5-52^\circ$ . The difference is about  $5.5-6^\circ$ . After heating maltase one hour at  $45^\circ$  its inactivation is considerable or very slight, but very marked at  $50^\circ$  for one hour. Inactivation rises about 50% by heating one hour at  $55^\circ$ , but at  $60^\circ$  for one hour the activity sinks to zero. Also, on heating ptyalin inactivation takes place very rapidly between  $55$  and  $60^\circ$ . Only 10% of the activity remains after heating one hour at  $60^\circ$  with optimal acidity and in the presence of an optimal amount of sodium chlorid.

Inactivation of maltase does not proceed as a monomolecular reaction, the velocity of inactivation diminishes more rapidly than demanded by the formula  $kO=1 \div kt$ . This accords with facts observed with saccharase. In the case of ptyalin of optimal acidity and in the presence of an optimal amount of sodium chlorid, inactivation velocity also sinks more rapidly than required by the aforementioned formula. It is certain, at any rate in slight dilutions that inactivation velocity increases with diminishing enzyme concentration. The reaction velocity is reduced 30% by diluting the enzyme from 1:1 to 1:5. Hence, ptyalin solution once inactivated can not be reactivated.

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#### The Problem of Zymase Formation in Yeast. I.

*F. Hayduck and H. Haehn, Biochem. Ztschr., 128: 558, Berlin, March 28, 1922.*

Since Buchner separated zymase from living cells and effected  
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the decomposition of sugar into alcohol and carbon dioxide with that agent, this process was ascribed to the enzyme zymase. Von Euler, however, propounded a working hypothesis of 2 species of enzymes, a free one and one confined to living protoplasm. He regards the zymase in the cell as a chemical complex combined wholly or partially to protoplasm. If the cell's vital activity is permanently or temporarily abolished, the fermentative protoplasmic group, i. e. the zymase confined to protoplasm, is also reactivated. Only that part of the fermentative enzyme which is liberated in the dehydration of yeast in vacuo or with alcohol, remains active. A hypothesis was propounded in respect of beer-yeast and spirit-yeast, the former of which forms zymase while the latter does not. Beer-yeast lives under cultural conditions that permit only slow multiplication. As a result of almost complete exclusion of air, the yeast is compelled to form zymase for sugar cleavage, as a source of energy; and, as adequate nutrient substances are present, so much zymase is formed that a part of it can be separated as free zymase. Spirit-yeast is cultivated under aëration with a view to cell multiplication. Here the yeast is compelled, first of all, to form plasma from the nutrient substances for propagation and only so much zymase will be formed as suffices for maintenance. In this case, therefore, only combined zymase will be found. If spirit-yeast were nourished richly and multiplication restricted by very weak aëration, this yeast would also have to form free zymase, and active zymase preparations could thus be obtained.

To demonstrate this, a series of experiments were undertaken: (1) Preparation of press-juice and permanent acetone products from pure cultures of brewer's yeast obtained by the aëration method. Both must be inactive. (2) Living yeast as in 1 mixed with sugar solution in toluol. No fermentation must take place. (3) Bottom beer-yeast must yield active pressed yeast and active permanent acetone products. (4) Spirit-yeast cultivated without aëration in rich nutrient solution must yield active zymase juice as well as an active permanent acetone product (formation of free zymase). (5) The same living spirit-yeast mixed with toluol in sugar solution should give no, or only weak, fermentation. (6) If bottom beer-yeast is shaken with toluol, poisoning of the plasma and formation of an emulsified layer around the plasma canal sets in. If the toluol is then removed with acetone an active permanent yeast product with free zymase must be formed. The experimental procedure is as follows: 10 gm. beer-yeast are shaken with 400 c.c. 10% cane-sugar solution and 5 c.c. toluol and immediately cultivated for 3 hours to determine germinative power. Germinative power should have disappeared or must be weak as compared to normal germinative power. Another yeast sample of 50 gm. is shaken for 3 hours in a corresponding volume of water with 25 c.c. toluol, then is syphoned off and converted into permanent acetone yeast. This preparation must not have diminished in strength in comparison to permanent yeast prepared from fresh yeast. Hereby it was proved that though toluol is capable of preventing fermentation of living yeast temporarily, it does not cause endotryptase to destroy free zymase, as assumed by Buchner. (7) Spirit-yeast contains only plasma zymase. This should be influenced as easily as plasma. If plasma is poisoned, not by an enzymatic poison, but by a plasma poison, fermentation ceases; on removing this poison,



sugar cleavage again sets in. (8) Living brewer's yeast should show only the fermentation of the free zymase with plasma poison; after removal of the disturbing body full fermentation should again set in. The experiments confirm the supposition that the reaction of the combined zymase is abolished by the poisoning of the plasma by the hydrocarbon and that free zymase is thereby prevented from becoming active. The latter is due to the fact that the toluol absorbs the cell's lipoid membrane until this solution forms an emulsified layer around the cell-content with the penetrating sugar solution so that the later reaches the zymase only sparingly.

A torula yeast species possessing very feeble fermenting power was employed for experiments on the following lines: (1) Germinative power of the yeast, i. e. fermenting of living yeast in the first 2 hours after commencement of fermentation. (2) Fermentative power of the yeast, i. e. evolution of carbon dioxid in the first 24 hours (free zymase and combined zymase of living yeasts). (3) Fermentative power of the free zymase; i. e. in like manner with the preceding, the fermentative power of the enzyme that still decomposes sugar in the killed cell in the presence of toluol. According to Pasteur, fermentation can replace respiration to a certain extent when, by means of prolonged adaptation, the yeast is rendered capable of altering its enzymes which participate in sugar decomposition. Accordingly, it should be possible to increase fermentation, and therefore the yeast's zymase content, by hindering respiration as is actually the case.

The experiments were carried out in such a manner that the yeast was gradually forced, by means of new vital conditions, to assume partly different metabolism. In cultivation without access of air, it was desired that torula should satisfy its energy requirement by zymase fermentation instead of by respiration (oxidation enzymes). It was found that catalytic action is absent with increasing zymase content. The cultivation experiments established the fact that zymase-deficient torula yeast may be transformed into yeast rich in zymase by means of lack of air. The nutrient solution for cultivation consisted of 100 gm. molasses, 10 gm. ammonium sulphate, 12 gm. superphosphate and 0.5 gm. magnesium sulphate. The experiments also showed that nitrogen content is not related in any way to the germinative power. Actually, therefore, the authors succeeded in cultivating a yeast with a high germinative power from a very weak strain (torula). The amount of the germinative power of a high culture is frequently twofold or even threefold. Obviously plasma zymase was formed in the process as permanent yeast preparations do not induce fermentation. It is possible, therefore, to endow the wild torula yeast not only with the properties of spirit-yeast but also with those of brewers' yeast. Baking experiments with torula yeast yielded yeasts with good baking periods. No relation of the yeast's baking capacity to the albumin content could be determined.

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#### Nitrogen Nutrition of Yeast.

*Frederick K. Swoboda. J. Biol. Chem. 52:91, May, 1922.*

A study of the nitrogen content and yield of yeast was made under conditions where the vitamin factor could be controlled. Accordingly,  
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studies were carried out with a constant concentration of vitamin in media containing as nitrogen sources variously hydrolyzed protein, with and without the addition of certain amino-acids or several other nitrogenous compounds in various concentrations. The tabulated results show that yeast grows better in an asparagin-containing medium in presence of ammonium sulphate than in the absence thereof. Similar results were obtained with succinamid, succinimide, and aspartic acid. Continued acid hydrolysis decreases the value of edestin as a yeast nutrient, while mild hydrolysis improves it to a certain degree. Alkaline hydrolysis is more destructive than the acid hydrolysis. In the absence of hydrolyzed edestin cystin, histidin, glucosamin, and cystin in the presence of tyrosin, retard the growth of yeast, while in the absence of hydrolyzed edestin, tyrosin, tryptophan, lysin, and arginin slightly stimulate yeast growth. In the presence of hydrolyzed edestin, cystin, tyrosin, or cystin with tyrosin stimulate yeast growth. Tryptophan, prolin, lysin, and arginin act similarly, but to only a slight degree. The general tendency is toward a retardation in growth with increased concentration of the amino-acid.

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**The Influence of Lactic Acid on Lactic Acid Fermentation.**

*B. J. Holwerda, Biochem. Ztschr., 128: 465, Berlin, March 28, 1922.*

No agreement exists in the literature regarding the dissociation constant of lactic acid. Experiments were therefore carried out with different methods: (1) conductive capacity measurement of pure lactic acid solutions: (2) potentiometric pH estimation in mixtures composed of sodium lactate or calcium lactate with lactic acid; (3) diazo-acetic ester decomposition after Bredig. Four different preparations were employed, all of which were optically inactive. The most probable value obtained from all measurements was  $1.5 \times 10^{-4}$  (25°). The considerably different values obtained by Van Slyke, Baker and Buerkle are incorrect and probably accidental. In comparing different methods it was found that Bredig's diazo-acetic ester decomposition yielded a slightly too low value (8-12%) for the dissociation constant of organic acids. The cause is most probably to be found in the action of the ester on the dissociation of weak acids. Decomposition proved to be an exact reaction of the first order in all cases. The author also endeavored to prepare a whey that might be utilized without addition as a nutrient medium for lactic acid fermentation. With this object the constants of a number of strains of lactic acid bacteria belonging to the group of *Streptococcus lacticus* were determined in whey cultures. It was endeavored to ascertain whether the age of the cultures and the composition of the whey exercised an influence on the value of the constant. If the latter were independent of the kind of culture and the composition of the whey, the constant could be utilized to differentiate the strains. The bacteria employed were obtained by the ordinary plate method from milk spontaneously acidified at 25°C. It was shown that lactic fermentation in peptone whey is arrested by a definite amount of the undissociated lactic acid molecules, independently of the whey's buffer effect. The respective amount was repeatedly found to be constant with bacteria of different origin. The value of the constants are independent of the composition of the whey. The amount of undissociated lactic acid molecules that

arrest growth of lactic acid bacteria depends on unknown factors. The value of the constant is not the same at all times. No regular increase or decrease with the ageing of the pure culture could be observed. In an artificial nutrient medium the injurious amount of undissociated lactic acid molecules was not constant. The constant always showed a distinct course. It was not possible to prepare an artificial nutrient medium for the determination of the constant. The physiologic action of the undissociated molecules was shown to be independent of the optical modification. The growth of a d-lactic acid-forming bacterium is arrested by a definite quantity of lactic acid molecules, whether they have the d or the l form. The dissociation constants of the 2 forms of lactic acid as was to be expected, are nearly or entirely equal.

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**A Method for the Determination of Small Amounts of Lactic Acid.**

*S. W. Clausen. J. Biol. Chem. 52:263, May, 1922.*

For the determination of lactic acid in pure solutions Clausen used two lactic acid standards, both prepared from a commercial brand of lactic acid, i. e. i-lithium lactate and i-zinc lactate, the latter being used in the majority of the experiments. It was prepared by adding the calculated amount of zinc chlorid in solution to lactic acid previously neutralized with NaOH. The product was recrystallized 4 times. It was free of chlorid and its ZnO content was 27.32%; theoretical for Zn ( $C_3H_5O_3$ )  $3 H_2O$  is 27.36%. A 0.1 n. solution contains 14.88 gm. per liter. The reaction is carried out in a pyrex glass tube  $20 \times 200$  mm. A straight inlet tube drawn to a capillary extends nearly to the bottom. The outlet tube is joined directly to a 40 cm. air condenser which, in turn, leads to the two receiving tubes. A rapid current of air is maintained by an aspiration pump. For carrying out the reaction 2 methods were tried. The first, a micro adaption of the von Furth-Charnass procedure. The reaction tube, containing 5 or 10 c.c. of 1%  $H_2SO_4$  and the lactic acid to be estimated, is placed in a water-bath heated to  $95^\circ$ ; the receivers each contain 20 c.c. of 0.02 n.  $NaHSO_3$ . While a fairly rapid air current is passing, 0.005 n.  $KMnO_4$  is added through the inlet tube, drop by drop; only as rapidly as it is decolorized. Water is added to preserve the original volume. After about half an hour, the permanganate no longer fades and the reaction is complete. The air current is run for ten minutes longer. The contents of the receiver are then transferred to a flask and the bound aldehyde is determined. The yield is about 92% of the theoretical. A modification of the method has been applied to analysis of blood and urine for lactic acid.

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**Chemical Constituents of Green Plants. The Acids of the Rowan Berry (*Sorbus Aucuparia*) Precipitable by Lead Acetate.**

*Hartwig Franzen and Rudolf Ostertag. Hoppe-Seyler's Ztschr. f. physiol. Chem., 119:150, Berlin, April 20, 1922.*

The juice of the rowan berry is the commonest source of l-malic acid. Another malic acid was detected by various investigators in Crassulaceae, the so-called crassulaceae-malic acid, which differs from

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rowan berry malic acid in not crystallizing even in the form of its salts. It is probable that the latter was contaminated by considerable quantities of other substances whereby crystallization was presented. In this case, however, not many other acids can be present in the rowan berry that would render its preparation in the pure state difficult. To elucidate these conditions, the acids were precipitated with lead acetate, the acids obtained from lead precipitates esterified and the esters subjected to fractional distillation by Schuhmacher's method. From percentage yields it may be concluded that the rowan berry acids precipitable by lead acetate consists of 99.5% malic acid. Malic acid, or its esters derived from the various extracts, received an addition of hydrazin hydrate and the dihydrazid was indentified by the melting point 178-179°. All acids precipitable by lead acetate and extractable with ether consisted exclusively of malic acid. Traces of citric and succinic acids were probably present. Liebig's contention that tartaric and citric acids occur in considerable amounts in these berries is therefore incorrect.

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**The Action of Muscle Tissue on Fumaric, Maleic, Glutaconic and Malic Acids.**

*H. D. Dakin, J. Biol. Chem., 52:183, May, 1922.*

Recent experiments on the oxidation of succinic acid by muscle extract made by Einbeck led the latter to conclude that the reaction proceeds primarily with the formation of fumaric acid and that the latter acid, by means of a balanced reaction, is converted into optically inactive malic acid to the extent of about 75%. Dakin repeated Einbeck's experiments and found that the enzymes of muscle tissue convert salts of fumaric acid into optically active malic acid. The levo variety was exclusively formed as opposed to Einbeck's statement that inactive malic acid is produced. Maleic acid under similar conditions gives no optically active malic acid, while glutaconic acid gives a little symmetrical B-hydroxyglutaric acid. On subjecting inactive malic acid to the action of muscle enzymes, the residual malic acid contains an excess of the dextro component, while some fumaric acid is produced. It would appear that the levo component is more readily converted into fumaric acid than the dextro component. The author's attempt to effect an asymmetric synthesis of active malic acid by the action of mercury i-lactate on malic acid was unsuccessful.

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**Lignoceric Acid and Its Derivatives.**

*Percy Brigl and Edgar Fuchs, Hoppe-Seyler's Ztschr. f. physiol. Chem., 119:280, Berlin, April 20, 1922.*

The highest members of the fatty acids, such as behenic and lignoceric acids, have been little investigated. Only the constitution of behenic acid (n-docosanic acid),  $\text{CH}_3(\text{CH}_2)_{20}\text{CO}_2\text{H}$  is known. From behenic acid m-tetracosanic acid,  $\text{CH}_3(\text{CH}_2)_{22}\text{CO}_2\text{H}$ , was built up synthetically and this acid was found to occur extensively as lignoceric acid, melting point 78-81° C. in beech-tar, and carnauba acid, melting point 72.5°, in carnauba wax. The former is found in oil of peanut, decaying oak, peat and in connection therewith in coal-tar, in

the animal world in the examination of cerebral substances, namely, in the oxidation of so-called cerebronic acid. Synthetic tetracosanic acid differs greatly from the natural products and melts at  $85^{\circ}$ . The authors therefore attempted to prepare lignoceric acid from beechwood and showed that it is not a mixture of acids with different molecular weights but one of two isomers, one of which is wholly identical with synthetic lignoceric acid. Its structure is probably the spiral one suggested by Klimont.

To elucidate the constitution of the isolated constituents of beech-tar, of lignoceric acid with high melting point, alcohol and lignocerin, the respective substances were synthesized with normal carbon chains and compared with the natural products. Original material for these experiments was the unsaturated acid of the series 22, erucic acid, which is obtained comparatively easily from rape oil. It was reduced to behenic acid and synthesized according to the following scheme: docosanic acid  $\rightarrow$  docosyl alcohol  $\rightarrow$  docosyliodid  $\rightarrow$  docosylmalonic acid  $\rightarrow$  docosylacetic acid = n-tetracosanic acid. The phenyl ester was employed instead of the alkyl ester. A crude beechwood tar paraffin was employed, namely, two tars forming brownish black, viscous masses whose solid parts consisted of bright waxlike plates. The solid parts are easily separated from the oily ones owing to their difficult solubility in cold acetone. To separate lignoceric acid the lead salt was prepared and thereby neutral substances could be separated from the acid. The yield amounted to 2-6%. The analysis of crude lignoceric acid gave the formula  $C_{24}H_{48}O_2$ . Lignocerin may be easily separated from the ethereal extract of the lead salt by reason of its difficult solubility and recrystallized from acetic ester it forms mother-of-pearl-like crystalline laminae melting at  $74-75^{\circ}$ .

Lignocerin has the formula  $C_{48}H_{96}O_2$ . It is the lignoceric acid ester of lignocerin alcohol. For the better characterization of lignoceric acid, its methyl and phenyl esters were prepared. The former melts at  $60^{\circ}$ , the latter at  $69^{\circ}$ . The wax is also a mixture. Its acid component contains lignoceric acids with low, and with high melting point. Lignocerin alcohol, a primary alcohol  $C_{24}H_{50}O$ , also possesses several melting points, but its analytic composition is always that of a tetracosanol. Potassium converts it into lignoceric acid with low melting point. The newly prepared n-tetracosanol-1, whose acetate and benzoate were described, has not so far been identified with a fraction of lignoceric alcohol.

The synthesis of waxes was also attempted, the principal constituent of spermaceti, cetyl palmitate, being built up. For this purpose 2.3 gm. cetyl alcohol were dissolved in 10 c.c. chloroform and 1.7 gm. quinolin, 3.8 gm. chloropalmitic acid, and 5 c.c. chloroform added. The amounts of quinolin and chloropalmitic acid are larger than the calculated ones to prevent the continued presence of unaltered alcohol besides wax after completion of the reaction. The mixture was allowed to stand under water cooling twenty-four hours at room temperature. Quinolin was removed with dilute acids. Palmitic chlorid was converted into palmitic acid by liquefying with water and the acid precipitated by calcium acetate. Finally the wax is recrystallized with chloroform. It had a melting point of  $53^{\circ}$ . Waxes of the  $C_{22}$  and  $C_{24}$  series may be prepared in an analogous manner.



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**The Synthesis of A-Hydroxyisopentacosanic Acid and Its Bearing on the Structure of Cerebronic Acid.**

*P. A. Levene and F. A. Taylor, J. Biol. Chem., 52:227, May, 1922.*

The authors have tabulated all the melting-points of the intermediate and final products prepared, respectively, from lignoceric acid and tetracosanic acid obtained from cerebronic acid. The derivatives of fatty acid included in the table are:  $\alpha$ -bromolignoceric acid,  $\alpha$ -hydroxy-lignoceric acid, isotricosanic acid, ethyl isotricosante, isotricosyl alcohol, isotricosyl iodid, diethyl isotricosyl-malonate, isotricosyl-malonic acid, lignoceric acid, ethyl lignocerate, lignoceryl alcohol, lignoceryl iodid, lignoceryl cyanid, isopentacosanic acid,  $\alpha$ -bromoisopentacosanic acid,  $\alpha$ -hydroxyisopentacosanic acid, ethyl isopentacosante, isopentacosyl alcohol, isopentacosyl iodid and isopentacosane. The tabulated results show that the melting-points of the dl-cerebronic acid prepared either from lignoceric acid or from tetracosanic acid obtained from cerebronic acid, melted at 92.5° C. The original cerebronic acid had approximately the same melting-point as the cerebronic acids described by Thierfelder and by Brigl. The melting-point of the inactivated cerebronic acid is given by Brigl 97°-100° C. From this he attributes to cerebronic acid the structure of the normal acid for which the melting-point is 102°-104° C. On the basis of the results described here it is evident that Brigl has not succeeded in inactivating cerebronic acid by his process. In fact, the authors think the observation that the melting-point lagged between 97°-100° C. casts a suspicion on the purity of his substance. Also the normal hydroxypentacosanic acid, if it were pure, should be expected to melt more sharply than at 102° to 104° C. Levene and Taylor claim the data furnished by Brigl may be entirely disregarded in considering the structure of cerebronic acid, and as evident from their present work, this is  $\alpha$ -hydroxylignoceropentacosanic acid.

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**On Some New Color Reactions of Cholesterol.**

*Louis Kahlenberg, J. Biol. Chem., 52:217, May, 1922.*

In the course of some investigations on the function of cholesterol in the animal body, the author found this substance was readily soluble in quite a number of anhydrous inorganic chlorids and bromids. In addition cholesterol, ischolesterol, phytosterol, and lanolin were found to dissolve in quite a number of anhydrous inorganic chlorids. In  $\text{PCl}_3$ ,  $\text{POCl}_3$ ,  $\text{SnCl}_4$ ,  $\text{SiCl}_4$ ,  $\text{SiBr}_4$ , and  $\text{CBr}_4$ , these solutions are all colorless. In  $\text{SOCl}_2$ ,  $\text{TiCl}_4$ ,  $\text{SeOCl}_2$ ,  $\text{SbCl}_3$ , and  $\text{AsBr}_3$ , colored solutions are formed. With  $\text{SbCl}_5$ , brownish masses are obtained. These reactions were not found to be sufficiently characteristic to enable them to be used to distinguish between the different substances dissolved. In  $\text{AsCl}_3$ , brain cholesterol or gall-stones cholesterol dissolves, yielding a pink solution which gradually turns to a bright cherry-red on standing, more rapidly on heating. Isocholesterol yields a cobalt blue solution which changes to violet, then to purple, dark red, and dark green on standing; more rapidly on heating. Phytosterol yields colorless solutions in  $\text{AsCl}_3$ . These reactions can be used to distinguish between



cholesterol, isocholesterol, and phytosterol. The color of all these solutions may be discharged by adding solvents like benzene, toluene, or chloroform.

Concentrated aqueous solutions of  $\text{AsCl}_3$  (in the presence of a large excess of  $\text{HCl}$ ) also give the color reactions with cholesterol or isocholesterol on boiling. On standing, the colored layers, which separate out on the bottom of the test-tubes gradually suffer hydrolysis, becoming colorless, the sterol separating out. The reaction is best obtained by dissolving cholesterol or isocholesterol in anhydrous  $\text{AsCl}_3$ . From the concentrated colored solutions of cholesterol in  $\text{AsCl}_3$ , cholesterol separates out practically quantitatively on standing at sufficiently low temperatures.

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**The Effect of Agitation on Human and Cow's Milk.**

*Hans Behrendt, Biochem. Ztschr., 128:450, Berlin, March 28, 1922.*

Milk is a mixture of dissolved and suspended crystalloid and colloid organic and inorganic substances and emulsified lipoids. It is therefore difficult to determine the physiochemic structure of this complex. By means of constant measurement, the authors attempted to study milk in the pathologic condition produced by mechanical agitation and to carry through an analysis of this alteration of the complex, i. e. of the reactions of the individual components, taking into consideration their correlation. Engel and Eufinger already showed that the titratable acidity of cow's milk undergoes no alteration after several hours' agitation, whereas human milk fixes 5-10 times as much alkali as before agitation. For this reason, and to elucidate the hypothesis of fermentative fat cleavage induced by agitation, the influences of (1) fat, and (2) temperature, of (3) the mutual exchange of various components of human and cow's milk, and (4) analytic determination of fatty acid, were utilized, in addition to stalagmometric investigations. Fat was estimated with Gerber's butyrometer and acidity determined with 2% alcoholic phenolphthalein solution as indicator. The degree of acidity occurring with agitation of human milk runs parallel to the fat content. Milk skimmed as much as possible does not acidify. The acidity of cow's milk and of skim-milk is not affected much by agitation. Here the lipase content is either too small or it is not active enough to incite such phenomena as are produced by the ferment in human milk. If the fat be removed from human milk, the ferment loses the material, or acidification is wholly or partially absent. If human milk is heated 2 hours at  $52^\circ \text{C}$ . or more, the increase of acidity during agitation is diminished. If cow's milk and human skim-milk are mixed in equal proportion, very strong acidity sets in upon agitation, which is absent when the skim-milk is previously heated to  $52^\circ \text{C}$ . When equal parts of human milk heated to  $52^\circ$  and freshly prepared human skim-milk are mixed, the effect of agitation is again obtained. As lipase is entirely destroyed by heating to  $65^\circ$ , acidification of every kind of milk by agitation is prevented by heating it 2 hours at  $65^\circ$  on the water bath. Although the cause of increased acidity due to agitation was already known, the author endeavored to determine, by these experiments, the fat cleavage products by means of the combined

vacuum and steam distillation methods of Bahrdt, Edelstein, Langstein and Welde. Water-soluble, volatile, lower fatty acids were detected. It was determined stalagmometrically that these fatty acids and their soaps produce a strong reduction of surface tension in agitated human milk. The observed facts rest on the adsorption of the lipase of human milk from fat with subsequent fermentative lipolysis.

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**A Quantitative Study of the Adsorption in Solution and at Interfaces of Sugars, Dextrin, Starch, Gum Arabic and Egg Albumin, and the Mechanism of Their Action as Emulsifying Agents.**

*George L. Clark and William A. Mann, J. Biol. Chem., 52:157, May, 1922.*

The object of this research was to study by the most accurate known methods the behavior of 5 substances which, to a greater or less extent, act as colloid protectors or emulsifying agents, viz., sugars, dextrin, starch, gum arabic, and egg-albumin, throughout the greatest possible range of concentration, each alone, and, for the purpose of studying ion adsorption, in the presence of the following electrolytes: hydrochloric acid, sodium hydroxid, iodid, sulphate and bicarbonate, as respectively acid, base, liquefying or peptizing salt, precipitating or peptizing salt, and a biologically significant substance. Each dilution of each one of the five substances under investigation, alone and in the presence of each of the five electrolytes, was studied under the following heads: (a) surface tension at 25°; (b) interfacial tension between solution and benzene, and in some cases caprylic alcohol for purposes of comparison between aromatic hydrocarbon and long chain alcohol; (c) viscosity; (d) density; (e) actual observations upon emulsions made up uniformly with benzene and kerosene and studied for heaviness of creaming and stability as measured by time of existence.

Surface tension was determined by the drop-weight method (Morgan apparatus); interfacial tensions by a modified Harkins and Humphrey drop volume apparatus; relative viscosities by a special Ostwald viscosimeter, and density at 25° by a Westphal balance. The results of experiments on each of the 5 substances are given in detail and elaborately tabulated. They show that viscosity and ability to lower the interfacial tension (especially viscosity) are of predominating importance in sugar as an emulsifying agent; that the inversion of sucrose is accompanied by a slight increase in surface tension; that dextrin is of the same chemical nature as starch but with smaller homogeneous particles; that dextrin is a better emulsifying agent than starch (viscosity here, however, being of secondary importance to the lowering of interfacial tension). Lowering of interfacial tension and viscosity are favorable for gum arabic solutions, while efficiency of egg-albumin is related to adsorption of film formation. Better emulsions were obtained with egg-albumin than with any of the other 4 substances. No one general rule can be made as to the effect which produces the best emulsions for any one substance, nor can any one generalization be made for the effect which produces best emulsions for all substances under all conditions. Those which seem to be of predominating importance are viscosity and film formation, the latter being of primary importance.

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**A Colorimetric Method for the Determination of Small Amounts of Magnesium.**

*F. S. Hammett and E. T. Adams, J. Biol. Chem., 52:211, May, 1922.*

The authors' method as used on solutions of bone-ash is as follows: From 5 or 10 c.c. (depending on the weight of the bone-ash obtained on incineration and the dilution of the solution made therefrom) of the clear supernatant liquid from the precipitation of calcium according to Kramer and Tisdall, are pipetted into a 30 c.c. beaker and 1 c.c.  $(\text{NH}_4)_2\text{HPO}_4$  solution, prepared according to the method of these workers, is added, drop by drop, and then 2 c.c.  $\text{NH}_4\text{OH}$ , similarly. After standing over night the precipitate is filtered through asbestos in a 27 mm. Gooch crucible with mild suction, washed 10 times with 5 c.c. lots of 10%  $\text{NH}_4\text{OH}$  solution, and twice with 90% ethyl alcohol, made alkaline with  $\text{NH}_4\text{OH}$ . The crucible is replaced in the beaker and dried in the oven at  $80^\circ\text{C}$ . for a few minutes. Then 10 c.c. 0.01 N HCl are added to the contents of the crucible in the beaker and the whole is allowed to stand for three hours at room temperature. The contents of the crucible and beaker are transferred to the test-tube and the asbestos is separated by centrifugation. Then 5 c.c. supernatant liquid are pipetted into a 25 c.c. graduated flask. Into a second 25 c.c. graduated flask there are placed 5 c.c. standard  $\text{KH}_2\text{PO}_4$  solution containing 0.05 mg. phosphorus. To both flasks are added 5 c.c. phosphate-free distilled water and 1 c.c. of the molybdic solution, 2 c.c. of the hydroquinon solution, and after five minutes, 10 c.c. of the carbonate-sulphite solution of Bell and Doisy. The contents of the flasks are then made to the mark with distilled water, and after standing from five to nineteen minutes, the unknown is compared with the standard in the colorimeter. The amount of phosphorus found in the test solution multiplied by  $0.7835 \times 2$  gives the amount of magnesium in the sample removed from the supernatant liquid from the calcium determination. The reduction of this value to terms of percentage in the bone varies from sample to sample according to the weight of ash, dilution of the ash solution, and the amount of material used for the calcium determination.

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**1c. PHARMACOLOGY AND TOXICOLOGY.**

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**Pharmacologic Classification in Relation to Practical Therapeutics.**

*P. Piccinini, Riforma med., 38:392, Naples, April 24, 1922.*

The best classification of drugs is that which divides them according to their therapeutic action. If it were possible to demonstrate a constant analogy between the physiologic action of drugs and their chemical constitution, the chemical classification would be the more rational; however, these relationships are not constant and, besides, the chemical constitution of many drugs, like the enzymes and hormones, is unknown. The physiologic classification of the drugs is therefore the best. The author has adopted in his manual a similar classification that he calls physiotherapeutic.

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**The Action of Tissue Diuretics.**

*H. Molitor and E. P. Pick, Wien. Wchnschr., 35:389, April 27, 1922.*

The author tested the diuretic action of novasurol, calomel, urea and caffein on winter frogs and frogs that had been approximated artificially to a warm-blooded type by means of heat. Novasurol and urea doubtless change the water-content of the tissues and are therefore to be regarded as tissue diuretics. Two phases can be distinguished in this process, water fixation, and water transportation from the tissues into the blood. With increasing temperature the two phases approach each other, so that in mammals they probably take place at the same time. When the tissues are already edematous probably the blood and tissue colloids capable of absorbing more fluid are the first point of attack, and they withdraw fluid from the already swollen edematous tissues. The edematization and disedmatization caused by various agents is not always due to the same process; the end condition of the disedematized colloid is of the greatest importance. With urea, which appears normally in the organism, there can hardly be any great degree of injury of the colloids, but novasurol may easily cause severe metal poisoning. The terminal condition therefore is different in the two cases. This may be the reason why edematization followed by disedematization results in diuresis in the one case while in the other it does not. Novasurol, calomel and urea cause a marked change in the tissues by processes of edematization and disedematization, while caffein does not have any marked effect of this nature on the tissue colloids of the frog.

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**The Action of Capsella Bursae Pastoris on the Uterus.**

*Wilhelm Wiechowski, Klin. Wchnschr., 1:786, Berlin, April 15, 1922.*

Haffter and Zondek believe that the action of shepherd's purse on the uterus is due to a parasitic fungus, *Cystopus candidus*, which is found on it. The author demonstrated that the action of *Capsella bursae pastoris*, *Secale cornutum* and *Ustilago maidis* is considerably increased by allowing their aqueous suspensions to stand; this is accompanied by the active development of gas and acids and an increase in the schizomycetes which are found in these drugs. Therefore it is assumed that the substances that act on the uterus are the products of bacterial cleavage which occurs partly in the living plant. A similar phenomenon was observed in *Agaricus muscarius*; under similar conditions a substance was formed which caused contraction of the uterus. The substance in *secale* that act on the uterus have nothing to do with histamin and tyramin which are also produced by bacterial action. Experiments on this subject are not yet finished.

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**A Note on the Action of Curare, Atropin, and Nicotin on the Invertebrate Heart.**

*A. J. Carlson. J. Gen. Physiol., 4:559, May 20, 1922.*

In this work the alkaloids used were of Merck manufacture and  
(Sec. 1—Page 97)

the species of invertebrates studied were molluscs (Octopus, Loligo, Ommastrephes, Mytilus, Mya, Tapes, Platydon, Venus, Pecten, Cryptochiton, Lucapina, Haliotis, Natica, Sycotypus, Aplysia, Bulla, Pleurobranchoea, Montereina, Triopha, Limax, Ariolimax, and Hellix), and arthropods (Palinurus, Cancer, and Limulus). Carlson found that in molluscs and arthropods (curare, atropin and nicotin) stimulate and paralyze the central nervous system and peripheral (visceral) ganglia, but do not paralyze the motor nerve endings to skeletal or visceral muscle. They stimulate and paralyze the denervated heart and paralyze or block the cardio-inhibitory nerves, but not the cardio-accelerator nerves. In the Limulus heart these drugs act primarily on the heart ganglion, not on the heart muscle or the intrinsic motor nerve fibers.

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**Exchange between the Blood and Tissues. II. The Influence of Adrenalin, Extracts of Hypophysis and Other Endocrine Gland Extracts and of Drugs Which Act on the Blood-Vessels.**

*Julius Bauer and Berta Aschner, Ztschr, f d. ges. exper. Med., 27: 191, Berlin, April 8, 1922.*

Several authors have observed increased density of the blood after giving adrenalin. The mechanism is not entirely clear. While some say that there is a stronger filtration of blood fluid into the tissues, caused by the contraction of the vessel walls, others deny any connection between rise of pressure and increased density of the blood. Possibly a change in permeability of the vessel wall plays a part in the process. Ellinger holds that the dilution of the blood that occurs later is due to the fact that adrenalin increases the edematization pressure of the albumin bodies in the blood. The authors' own experiments showed that adrenalin frequently causes changes in the albumin concentration of the blood. There may be either dilution or increased concentration. Which of these processes takes place does not depend on the time after injection, for sometimes one and sometimes the other precedes. The changes in serum concentration (which do not always correspond to the changes in the erythrocyte count) are not connected with the rise of blood pressure nor are they parallel with the sodium chlorid content of the serum. When a decrease of permeability of the capillaries has been brought about by adrenalin, it is not sufficient to check a movement of fluid, such as is caused by injection of a hypertonic solution; hydremia occurs in spite of the adrenalin. The fact that adrenalin acts on the coagulability of the blood, the blood sugar content and increase of albumin metabolism, explains why its action on the concentration of sodium chlorid and albumin in the serum varies, depending on the individuality and susceptibility of the individual organs. The action of extract of hypophysis on serum concentration consists in the production of hydremia. According to Veil, extracts of hypophysis have an extrarenal action; they make the tissues capable of retaining an increased amount of water. According to Oehme their action is renal. As the authors found in a case of diabetes insipidus that the fluid exchange between the blood and tissues was the same after pituitrin as under normal conditions, they think Veil's theory is disproved. E. Meyer and R. Meyer Bisch found that a dog with a fistula of the

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thoracic duct had less lymph when acted upon by pituitrin. This would prove the extrarenal action, if intestinal peristalsis and inhibition of gland secretion did not forbid that conclusion. The authors' experiments showed that extract of hypophysis does not always cause hy-dremia. The same is true of the sodium chlorid content of the blood. At any rate the inhibited kidney function and the changed activity of some glands may influence the composition of the blood secondarily. Nor in experiments with thyroid, testicle, pineal gland and ovarian extracts was a uniform effect on the composition of the blood found. On the other hand, there was a tendency to dilution of the blood after injection of quinin and in 3 cases after papaverin injection. Different results were obtained with colchicin. Possibly the results obtained with drugs that act on the vessels are due to hypertonia in the person experimented on. On the injection of pilocarpin the concentration of the serum increased, but that of sodium chlorid remained the same, in a case of chronic nephritis.

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**The Pharmacologic Action of Adrenalin on the Sphincter Pylori of the Fetus.**

*P. G. Shipley and K. D. Blackfan, Bull. Johns Hopkins Hosp., 33: 159, May, 1922.*

It has recently been suggested by Pirie that the condition of hypertrophic stenosis of the pylorus in infants might be due to fetal hyperadrenia. The idea is that reflex stimuli (in Pirie's theory arising chiefly from the prepuce) might lead to adrenal overactivity and thus produce pyloric hypertrophy from adrenalin action upon the smooth muscle of the pylorus. This theory assumes the so-called reversed innervation of the gastro-intestinal sphincters, i.e. that the pyloric and ileocolic sphincters are augmented through the splanchnic nerves and depressed by way of the vagus, in contradistinction to the bulk of the intestinal musculature. Shipley and Blackfan claim that this theory is not founded upon observation, since almost nothing is known about the behavior of the intestine during intra-uterine life. They have been studying the physiology of the gastro-intestinal tract in the fetus, and are able to present direct evidence of what happens when adrenalin is brought into contact with the pyloric sphincter, both in pig fetuses and in the human. The experiments were done both in vitro upon isolated strips and in the body with the pyloric innervation and blood-supply intact. The result of applying adrenalin to the pyloric sphincter is an inhibition and relaxation. Increased secretion of adrenalin can hardly result in anything else than a decrease in tone of the pyloric musculature. Furthermore since the action of adrenalin on the muscles of the gastro-intestinal tract depend on stimulation of the endings of the splanchnic, reversal of valvular innervation, if it exists in the adult intestine, must be a phenomenon confined to a postfetal life. Therefore hypertrophic stenosis cannot be explained upon the basis of Pirie's theory.



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**The Cardiovascular Action of Pepsin.**

*Locper and Mougcot, Bull. et mém. Soc. méd. d. hôp. de Paris, 38:721, May 11, 1922.*

Blood pressure during digestion first decreases and then increases. This initial hypotension seems to be due to the passage into the circulation of certain substances secreted by the mucosa of the gastro-intestinal tract, which have the property of lowering the blood pressure. Among these pepsin has an important rôle which was specially studied on several patients. The administration by mouth of 1 gm. pepsin on an empty stomach had no effect on the arterial tension, but hypodermic injections of 0.20 gm. produced a marked fall of both the maximal and minimal readings, while the pulse pressure remained unchanged. The fall recorded was 2-4.5 cm., being highest in cases of hypertension. It is apparent 5 minutes after the injection and begins to disappear after 1 hour. In only 1 patient was an increase of pressure noted. Intravenous injections of pepsin produced symptoms of shock in the same patient, but not in the others, who reacted in the same way as with hypodermic injections. There is therefore no reason to prefer the intravenous method of administration. No signs of sensitization were noted in the patients who had previously taken pepsin by mouth. Similar experiments made with the same doses of peptone showed that this substance has no effect on the circulation and produces no symptoms of shock when it is injected hypodermically, while intravenous injections is nearly always followed by shock.

In dogs the intravenous injection of 2 cg. pepsin per kilo of weight produces a fall of blood pressure of 4 cm. When, however, 1 mg. atropin per kilo was previously given, as much as 6 cg. pepsin could be administered without affecting more than very slightly the blood pressure curve. It seems, therefore, that pepsin acts through the medium of the vagus. In view of these experiments the therapeutic use of pepsin as a hypotensive drug may be contemplated in the future, for its effect is quite marked as that of the best hypotensive remedies known, and in individuals having a high blood pressure the results produced are particularly prolonged. Several injections seem, moreover, to have a cumulative effect.

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**The Pharmacology of the Lipoids. II. Soap and Serum.**

*Adolf Jarisch, Pflüger's Arch. f. d. ges. Physiol., 194:337, Berlin, April 20, 1922.*

Erythrocytes washed in NaCl solution experience an increase in their resistance to hypotonia in lipid solutions or in soap solutions of low enough concentrations not to produce hemolysis. Experiments were made to see whether the same thing is true in the presence of serum. It was found that with increasing amounts of soap there was first a rise and then a fall in resistance to hypotonia, and finally spontaneous hemolysis, as in the experiments in NaCl solution, but with changed quantitative conditions, as the amount of soap required increased with increasing amounts of serum. An analysis of this process

shows that soap in the presence of serum is broken up hydrolytically into fatty acids and alkali, and the fatty acids combine with albumin to make a clear solution from which they can be precipitated again by acids or salt solution. If the serum is poor in salt there is a voluminous precipitation after the addition of soap, colloidal fatty acids, alcoholic organ extracts, cholesterin or commercial lechithin. There is a similar precipitation in salt-poor serum on the addition of saponin, bile, sodium desoxycholate, thymol, camphor, tributyrin and narcotics.

The precipitated body behaves like insoluble globulin, is soluble in salts and precipitates again on dilution with distilled water. The cause of this may be that the sensitiveness of the globulin to the precipitating action of the added substance varies with the salt content. In this way the lipoids may acquire an influence on the solubility of the globulins. The rise of the hypotonia resistance of the erythrocytes in serum also is due to the formation of this fatty acid-albumin compound. The disease in resistance which the erythrocytes undergo by washing in physiologic salt solution, is hardly perceptible in solutions free of carbonic acid, and is therefore due to the action of carbonic acid. Sodium bicarbonate acts on erythrocytes like an alkali, as it increases resistance to hypotonia and to heat; it moreover favors the flocculation under heat of stroma substance.

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**A Saponin from Agave Lechuguilla Torrey.**

*Carl O. Johns, Lewis H. Chernoff and Arno Viehovever, J. Biol. Chem., 52: 335, May, 1922.*

The material used in this investigation was obtained from Uvalde, Texas, and consisted of the rootstocks and short stems and attached leaves. The authors were able to isolate a saponin not hitherto described from the rootstock with attached roots and short overground axis, and the bases of the leaves of Agave lechuguilla. The results of the ultimate analyses, the molecular weight determination in phenol, the nature of the products of hydrolysis of the saponin, and especially the results of the analysis of the sapogenin suggested to the authors the formula  $C_{27}H_{44}O_{12}$ . The saponin was soluble in water, alcohol, and phenol. Lead acetate, lead subacetate, and barium hydroxide did not precipitate it from either the aqueous or alcoholic solutions, nor did cholesterol form an insoluble compound. The aqueous solution containing 100 mg. saponin per liter hemolyzed rabbit's blood in about one hour at 37° C. Its surface tension at 37° C. in Locke's solution was 59.75 dynes per centimeter.

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**Chemical Changes of the Blood under the Influence of Drugs.**

**I. Ether.**

*Harry V. Atkinson and Harold N. Ets, J. Biol. Chem., 52: 5, May, 1922*

This investigation attempts to correlate the changes in the blood constituents, under the influence of ether anesthesia. From the hearts of healthy dogs about 30 c.c. of blood were drawn (a) just before a

two-hour period of ether anesthesia; (b) just before removing the ether; (c) on the following morning. In this study, determination of sugar, H-ion concentration, carbon dioxid-combining capacity of the plasma, creatinin, total nonprotein nitrogen, urea nitrogen, total lipoids, cholesterol and lecithin were made on the same sample of blood. The tabulated results show the following definite changes: (1) The blood-sugar content during ether, also the H-ion value, is raised and the carbon dioxide capacity of the blood plasma is decreased. The cause of the rise in the sugar may be related to (a) the increase in the H-ion which corresponds to a decrease in the pH; and (b) the decrease in the carbon dioxid capacity of the blood-plasma. (2) The fat decreased during the ether narcosis and then showed an after-rise above normal. (3) The cholesterol and lecithin changed very little.

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**Effect of Cocain on the Growth of *Lupinus Albus*. A Contribution to the Comparative Pharmacology of Animal and Plant Protoplasm.**

*David I. Macht and Marguerite B. Livingston. J. Gen. Physiol., 4: 573, May 20, 1922.*

The authors investigated the influence of the following substances on the growth of lupine roots: cocain hydrochlorid, sodium benzoate, methyl alcohol, methyl benzoate, ecgonin hydrochlorid, benzoyl ecgonin, and various mixtures of these drugs. The procedure employed was as follows: The dry seeds were soaked over night in tap water at ordinary temperature. On the following day the swollen seeds were planted with the hilum downward in moist, finely ground sphagnum moss. The planted seeds are placed in a thermostat and left at a constant temperature of 20°. On the third day after planting, the roots of the seedlings are of convenient length for measurement and are ready for study. After recording the exact length of a root it is placed in an upright test-tube of hard glass containing nutrient solution, the seed resting on the upper edge of the tube. The solution employed was the so called Shive solution which contains calcium nitrate magnesium sulphate, and monopotassium acid phosphate. The normal growth of the lupine rootlets was studied by immersing the seedlings in a mixture of normal Shive solution with an equal part of distilled water. The effect of the substances enumerated above was studied by dissolving them in distilled water and mixing such solutions with equal parts of the normal Shive solution. After measuring accurately the length of each root and placing the seedlings in the control and drug solutions, the whole was again put in the incubator and left at a constant temperature of 20° C., and the effect of various chemicals on the growth of the roots was determined at the end of twenty-four hours. The tabulated results demonstrate that to produce complete inhibition in the growth of the plant a 2.04% solution of cocain is required. The lethal dose of ecgonin hydrochlorid for lupine roots was found to be a concentration of 0.55%. Benzoyl ecgonin was found to be much less toxic for lupine roots than ecgonin itself. Methyl alcohol was found to be not very toxic for lupine roots while sodium benzoate was found to be the most toxic of all the substances studied, a concentration of only 0.007% being sufficient to kill the plants.

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**Treatment of Cocain Intoxication in Animal Experiments.**

*Agda Hofvendahl, Ztschr. f. Hals-, Nasen- u. Ohrenhkl., 1:233, Munich, March 22, 1922.*

In experiments on dogs, cats, rabbits and guinea-pigs author attempted sufficiently to decrease the irritability of the cerebral cortex with hypnotics to postpone threatened symptoms of intoxication resulting from subcutaneous injection of fatal doses of cocain (increasingly frequent spasms and finally suffocation in a condition of tetanic spasm) until the toxin could be gradually destroyed or excreted. It has already been shown that the spasms are caused by irritation of the cortex of the cerebrum. These experiments have shown that among the narcotics the most effective in preventing the action of a fatal dose of cocain is sodium diethylbarbiturate. The drugs examined, including the one mentioned, and chloral hydrate and scopolamin hydrobromid, act more surely the sooner they are given and the quicker they are absorbed. Therefore intravenous injection is the only method to be used if spasms have already begun.

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**Action of Novocain on the Tonus of the Skeletal Muscles.**

*S. De Boer, Nederl. Tijdschr. v. Geneesk., 66:1621, Haarlem, April 22, 1922.*

In 1916, Meyer and Heiler reported a case of contracture of the abdominal muscles which persisted for 2 years after tetanus infection. Lumbar injection of 0.02 gm. stovain and intramuscular injection of curare failed to cure the contracture, but after intramuscular injection of 10-15 c.c. of 1% novocain solution the contracture disappeared without affecting the direct irritability of the muscle. It was maintained that the novocain had paralyzed the sensory and motor fibers. Later the same authors reported a case of tetanus with local contracture of the biceps, which was cured by novocain injection without abolishing the indirect irritability or voluntary contractility of the muscle. This indicated that the contracture did not depend on motor impulses, and that novocain might have a toxic action on the accessory end-plates. Liljenstrand and Magnus held that small doses of novocain poison the proprioceptors of the muscles without influencing the motor innervation.

With a view to determining what local action was involved in the effect of novocain, De Boer made a series of experiments on frogs. After the intramuscular injection of 2 drops of 1% novocain solution into the leg, the muscle tonus was abolished and no contraction could be induced by the subcutaneous injection of sodium sulphocyanate. The reverse was also true, i.e. contractions induced by a previous subcutaneous injection of sodium sulphocyanate were abolished by an intramuscular injection of novocain. An isolated leg was immersed in 2% sodium sulphocyanate solution; the muscles contracted within a short time, spreading the foot tensely. After immersion in novocain 1:1000 with 0.65% sodium chlorid, transfer to a solution containing 100 c.c. sodium chlorid, 2 gm. sodium sulphocyanate and 0.1 gm. novocain did not stimulate contraction.

These experiments and the findings of Frank, Riesser, Schüller and their co-workers tend to demonstrate that novocain in small doses poisons the receptive substance of the tonus substrate, and that sodium sulphocyanate in small doses stimulates this substance to contraction. Liljestrand's and Magnus's view that novocain poisons the proprioceptors of the muscles and thus abolishes the contracture or normal tonus is disproved. The experiments do not determine the nature of the receptive substance or of the tonus substrate, nor whether the latter is identical with sarcoplasm.

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**Studies of the Pharmacology of Strontium.**

*H. Boruttau and K. Grassheim, Ztschr. f. d. ges. exper. Med., 27:213, Berlin, April 8, 1922.*

Primarily the authors are concerned with the action of strontium on the nervous system. Injection of strontium frees the patient of pain in osteopathies. Melzer and Auer showed that nerves kept in isotonic, hypotonic or hypertonic solutions of magnesium no longer conducted sensation, but Grassheim showed that injection of strontium chlorid under the skin of a rabbit decreased the sensitiveness of the skin to faradic stimuli considerably in comparison with subcutaneous injection of sodium chlorid. A closer study of stimulability and conductivity in the nerves under the influence of strontium was made with the string galvanometer by registering the action current. The threshold of stimulation was determined by an opening induction current, i.e. a barely perceptible movement of the strings as a manifestation of a one-phase action current. Moreover to determine conductivity nerves were stimulated by induction currents whereupon tetanization and the phenomena of fatigue, which consist in a change in amplitude of the positive secondary oscillations of Hering, were noted. Keeping a nerve in Ringer's solution which contains strontium, decreases its conductivity in a short time. The process is reversible. A further study was made to see whether strontium acts also on the motor nerve endings. The femoral artery was ligated in frogs and strontium injected into the lymph-sac; then the sciatic nerve and the gastrocnemius muscles were stimulated. It was found that strontium slows conductivity in motor nerves. It has only a pseudocurare effect. Strontium does not have a paralytic action on the central nervous system. The sluggishness of the animals after treatment with strontium is due to its action on the sensory and motor peripheral nerves. This sluggishness continues for a long time in contrast to the effects of magnesium narcosis from which the animals awake quite lively. The electric stimulability of the cerebral cortex is not decreased by strontium. To test its action on the reflex tracts, frogs were decapitated and the normal reflex time determined by plunging them in 0.1 n. sulphuric acid. Then equimolecular solutions of sodium chlorid, calcium chlorid, magnesium chlorid and strontium chlorid were injected. It was found that double molecular solutions of strontium and magnesium chlorid have an inhibitory action on the reflex tracts. Strontium in weak solutions stimulates, in strong solutions inhibits, the irritability and contractility of the heart. On the other hand, secondary flutter



caused by the alternating current can be prevented by a preliminary injection of strontium. This effect is probably due to a lengthening of the duration of stimulation, and therefore of the refractory stage. Its action, therefore, corresponds to that of camphor. As strontium slows frequency, strengthens systole and increases blood pressure, and as it is slightly toxic, it can probably be used as a heart remedy.

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**A Pharmacologic and Pharmacodynamic Study of Strophanthins and Ouabain (Concluded).**

*M. Tiffenau, Bull. d. sc. pharmacol., 29: 244, Paris, May, 1922.*

Subcutaneously, ouabain is 1.5 times as toxic as crystallized strophanthin, the figures for the rabbit being 0.36-0.50 mg. for ouabain, and 0.50-0.66 mg., for strophanthin, per kg. body-weight. With the guinea-pig, the lethal dose is 0.28 mg.; for the mouse, 0.13 mg. It is difficult to compare the toxicity of ouabain and that of strophanthin Kombé. For the guinea-pig, the latter is more toxic than ouabain. The true toxicity of strophanthin does not always appear, since the drug is unstable. Given by mouth, or subcutaneously, it is less toxic than ouabain. The sensitiveness to ouabain in the cat, dog, rabbit, mouse and rat decreases in the order given. The author's findings for the dog and rabbit, with ouabain, are about the same as Hatcher's (0.175 and 0.20 mg., respectively). These results apply to intravenous administration. The toxicity present in the latter route is quite fixed, permitting adequate testing. Crystallized ouabain remains stable. Dilute solutions are not altered by sterilizing in the autoclave, when contained in neutral glass or mixed with saline diluents.

In order to avoid bulbar complications in dogs examined, the animals were anesthetized with chloralose, and kept alive with artificial respiration, the chest being opened. The auricular and ventricular beats could thus be recorded. Acute intoxication with ouabain occurs in 3 stages: (1) Slowing of the beat from the second to the fifth minute produced by vagal stimulation and prevented by sectioning the vagus. (2) Acceleration, with arrhythmia and dissociation of the type 3 auricular, to 4 ventricular, contractions. (3) Fibrillation, beginning in the auricle and soon followed by death of the heart, which dilates in a marked diastole. The quantity of ouabain toxic for the dog is that which produces cardiac arrest in 10-20 minutes, consisting of 0.14-0.15 mg. per kg. body weight. Some 30 dogs were examined. Ouabain, 0.12-0.14 mg. may produce death of the heart after a longer time than that mentioned above. Below 0.12 mg., the 2 first phases, but not the third phase, appear. Author's figures differ somewhat from results published by others. The differences are due to variations in technic.

The different brands or varieties of ouabain appearing on the market are practically uniform, with respect to physical, chemical and toxic characters. Ouabain may therefore be generally adopted for therapeutic use. Chemical and physical tests, and estimation of water of crystallization will secure the clinician. Intravenous tests in dogs and rabbits, or the estimation of the toxicity in frog-units, are not strictly necessary for ouabain, but are indispensable in determining the therapeutic value of amorphous strophanthins.



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**Carbon Tetrachlorid. A Drug Proposed for the Removal of Hookworms, with Special Reference to Its Toxicity for Monkeys When Given by Stomach Tube in Repeated Doses.**

*G. C. Lake, Pub. Health Rep. (U.S.P.H.S.), 37:1123, May 12, 1922.*

Carbon tetrachlorid has been found the most effective drug as an anthelmintic for hookworms in dogs and also the least toxic of any of the active vermifuges tried. Without evidence of discomfort, dogs withstood 1.5 c.c. per kilo body weight, or 5 times the amount (0.3 gm.) which was found, in a large series of tests, sufficient to ensure the expulsion of all the hookworms. Monkeys were treated with very large doses, even as large as 100 times the dose indicated for man, without any definite signs of intoxication. There is every indication that the use of carbon tetrachlorid in the treatment of hookworm in man is worthy of an extensive trial. It should be administered in 3 c.c. doses in hard gelatin capsules, after the patient has fasted over night. The capsules must be swallowed promptly, for if some of the drug should enter the trachea serious results might follow.

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**The Principles of the Biologic Disinfecting Power of Acridin Dyes, Especially Flavacid.**

*Hans Langer, Ztschr. f. d. ges. exper. Med., 27:174, Berlin, April 8, 1922.*

A peculiarity of acridin dyes is that the presence of dissolved albumin increases their activity. This increase grows with the size of the molecules, i. e. it is inversely proportioned to the dispersibility. The addition of serum decreases the dispersibility and therefore increases the action. The dispersibility and therefore the disinfectant action are decreased by the addition of acid and increased by the addition of alkalis. If the dispersibility is measured by its capacity for diffusion in gelatin the foregoing laws hold and it is found that  $A_4(C_{15}H_{15}N_2Cl)$  and dimethylamino-acridinium chlorid (=Di. A) are more diffusible than flavacid. The limit of action of flavacid with a neutral reaction was found at 1:600,000. But in practice the penetrative capacity of the disinfectant plays a great part, and is indeed a prerequisite for disinfection. Therefore the maximum action is found with the maximum penetrative capacity and capacity for adsorption. Moreover the distribution will depend on the nature of the bodies of the bacteria. A general characteristic of colloid disinfectants is their electivity, not observed in crystalloids. Colloid disinfectants act particularly on Gram positive bacteria. In practice generally the action of the disinfectant in inhibiting growth is studied. In the body, however, the contact between the disinfectant and the bacteria is brief, and therefore drugs which are rapidly excreted (as salvarsan) quickly decrease in concentration in the blood. A reversible process in the penetration of the disinfectant must be at the bottom of inhibition of development, while in bactericidal action the process has become irreversible. The more a disinfectant is adsorbed the less the reversibility. This is less in flavacid than in the other acridin derivatives. For therapeutic purposes it depends on the intensity of the action, that is whether the disinfectant is bactericidal in a short time. Flavacid

1:1000 kills staphylococci completely in ten minutes, and at 1:1,000,000 causes a marked decrease in the bacteria in an hour, when flavicid attains its maximum action. The quantity of bacterial material is also important in the action of disinfectants. The action of flavicid is largely independent of this factor, and if the number of bacteria is less than ten billion the quantitative factor does not affect it. Guinea-pigs were given subcutaneous injections of staphylococci and then flavicid 1:100,000 was injected around the bacteria. Suppuration did not occur or if present underwent retrogression. The signs of irritation which developed after subcutaneous injection could be avoided by intravenous administration. As the tolerated dose in rabbits is 2.5 cg. per kilo of body weight, there is a wide field for the therapeutic use of flavicid. The average dose of 1-2.5 mg. per kilo of body weight has been found harmless for infants. As to the danger of repeated injections, necropsy of a rabbit that had been given 3 mg. flavicid daily for a month showed no injury of parenchymatous organs. It had lost 200 gm. in weight. Leukocytosis was induced by the last injection as well as the first. Therefore leukocyto-genesis, an important therapeutic factor, was not decreased.

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**Study of the Action of Four Aromatic Cinchona Derivatives on Pneumococcus. A Comparison with Optochin.**

*Lloyd D. Felton, and Katharine M. Dougherty, J. Exper. Med., 35:761, June 1, 1922.*

Optochin has been shown to have a beneficial effect on experimental pneumococcus infections of mice, in which animals the bacteriotropism is greater than the organotropism coincident with it. The use of optochin in man has, however, proved unsatisfactory, and the experiments here reported were carried out to determine the efficiency of other related compounds as chemotherapeutic agents against the pneumococcus in comparison with optochin, the design being to find one more distinctly monotropic. A number of cinchona derivatives, certain of which possess a high bactericidal activity for pneumococci, were investigated. With one strain of pneumococcus (Type I, Neufeld), hydroquinin chloracetanilid (C 29), hydroquinin p-chloracetaminophenol hydrochlorid (C 36), hydroquinin m-chloracetaminophenol hydrochlorid (C 40), and hydroquinin 4-chloracetaminopyrocatechol hydrochlorid (C 110) were found to have a rapid pneumococcal activity both in vitro and in the peritoneal cavity of mice and, to a lesser extent, of rabbits. The action of optochin under similar conditions was slower, but its power was less easily destroyed.

The introduction of the hydroxy group of the benzene nucleus of hydroquinin chloracetanilid changed the relationship between organotropism and bacteriotropism. C 29 exhibited the most rapid pneumococcal action and was the most toxic for mice. C 36 was one-fifth as toxic as C 29 and only one-tenth less active bactericidally. C 40 was one-half as toxic and had approximately the same bactericidal power, C 110 was one-eighth as toxic and one-fifth as pneumococcal. Optochin was one-sixth as toxic and had one-fifth the bactericidal action. Arranged in the order of ability to kill pneumococci when injected simultaneously with them into the peritoneal cavity, the drugs stood: C 40, C 110, C 36, optochin, and C 29.

The chemotherapeutic action of the aromatic compounds is essentially local in character, but a certain amount of diffusion of this cavity occurred after administration by mouth. The natural defenses of the animal were somewhat destroyed by intravenous injection of the drugs in small doses, optochin being less injurious. The same destruction of natural resistance followed intraperitoneal and subcutaneous injections of the chemicals as measured by intravenous injections of the organisms. Repeated doses, in general, were found to be more curative than single massive doses. There is a zone between the therapeutic and toxic doses, both single and repeated, for all these chemicals alike, where the natural resistance of the animal to an infection is reduced. This effect is noted especially with C 29, C 36, and C 40. In the case of optochin the therapeutic dose is nearer the toxic than with C 110, C 36, and C 40. Apparently these chemicals exhibit a variability in bactericidal activity in vivo according to different strains of pneumococci and numerical virulence.

The final test of any chemotherapeutic agent is the determination that its use effects a cure of an established infection, and for such tests mice are unsatisfactory, because of the short incubation period of the pneumococcus and the rapid course of the infection. These experiments have shown, however, that good results are obtained when the pneumococci and the drugs are injected simultaneously, but that any delay in administration of the latter neutralizes their effect. The question whether these compounds have a therapeutic application in man cannot be answered until further studies have been made.

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### **The Influence of Alkalinity on the Effectiveness of Quinin Alkaloids.**

*I. Michaelis and K. G. Dernby, Ztschr. f. Immunitätsf. u. exper. Ther., 34:194, Jena, May 11, 1922.*

Quinin derivatives are more effective in vitro than in vivo. In order to explain this discrepancy the action of the alkaloids was studied at different hydrogen-ion concentration.

*Staphylococcus aureus* grows at pH 4-8.5, the most favorable being pH 7-8. In buffer solutions (sodium acetate and phosphate solutions) the bacteria live at pH 3.7-8.2 even after 6 days. To the aforesaid buffer solutions (1.8 c.c.), 0.2 c.c. eucupin dihydrochlorate (of varying concentrations) was added in order to study the solubility of the eucupin at different pH. The original pH was not markedly changed by the eucupin solution. At pH 5.5, the solubility of eucupin is 2:1000, at pH 7.4, 2:10,000, and at pH 8, 1:10,000. Buffer solutions at pH 7.4 were inoculated with staphylococci, kept at 37°C. for 24 hours after adding varying amounts of alkaloid and then a drop was streaked on agar. The smallest lethal dose of the various alkaloids were found as follows: optochin 1:1000; eucupin 5:100,000; eucupintoxin 2:100,000, and vuzin 1:100,000.

Using a constant eucupin concentration (2:10,000) the action of pH was followed from time to time. This showed that after 1 hour no noticeable effect was produced by eucupin, after 6 hours the eucupin was lethal at pH 6, and after 72 hours eucupin was lethal at every pH.

From these experiments it is concluded that the bactericidal effect increases with increasing alkalinity. The explanation for this is that only the free base of the alkaloid is toxic. The further testing of the effect of eucupin in bouillon showed that its bactericidal effect is not influenced by the albuminous mediums. In this series the same differences were found in the action of the individual alkaloids as in the experiments with pure buffer solution. All of these experiments tend to demonstrate that only the free bases of the alkaloids act as disinfectants, but not their salts or ions. For therapeutic purposes it is important to know at what pH the alkaloids act most favorably, as the pH of the blood, lymph and inflammatory tissues varies and therefore it is necessary to use different concentrations of the alkaloids to achieve biologic results.

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**Comparative Studies of the Relation of Quinin and Some of Its Derivatives to Different Hemolytic Processes.**

*Johannes Burmeister, Pflüger's Arch. f. d. ges. Physiol., 194: 182, Berlin, March 24, 1922.*

The drugs tested were quinin, quinin sulphate, quinin hydrochlorid, euquinin, aristochin, quinidin, and optochin; calcium chlorid and sodium chlorid were used as controls. Only quinin sulphate and optochin showed pronounced hemolytic action on the erythrocytes of man and sheep. With stronger concentrations and longer duration of action, quinin, quinin hydrochlorid and quinidin also had slight hemolytic action. This hemolysis can be prevented by the addition of a little acid. Comparison showed that in the hemolytic series beginning with calcium, quinin and sodium are on the same side. In greater, nonhemolytic dilutions, quinin strengthens the erythrocyte membrane. When another hemolytic agent and quinin salts are allowed to act at the same time, there is a superposition of their actions. If the erythrocytes are given a preliminary treatment with quinin salts, the effect is clearer and more intense, but there are complicated conditions present, for acid hemolysis is inhibited by quinin, while sodium hydroxid hemolysis is increased, and quinin hemolysis is inhibited by acids but is increased by sodium hydroxid. Quininized erythrocytes are sensitive to acids and non-sensitive to sodium hydroxid. Quinin hemolysis is inhibited by carbonic acid, while carbonic acid hemolysis is increased by quinin. Quinin inhibits complement hemolysis, increases thymol hemolysis, inhibits amyl alcohol hemolysis and increases saponin hemolysis.

The relation to sodium hydroxid and acid hemolysis is due to the action of the alkaloid character of the quinin. The effect of carbonic acid is due to the fact that the erythrocytes, as after preliminary treatment with quinin, remain acid-sensitive. The hemolytic action of quinin is parallel to its hydrolytic cleavage. The chief emphasis, however, is to be placed on the condition of the quinin-laden erythrocytes, which behave as if they were under the influence of acids. The author assumes a second hydrolytic cleavage of the alkaloid constituent, which on the one hand brings about an alkaline reaction and on the other hand through a positively charged quinin constituent leads to a rupture of the colloids of the cell membrane which are the point of attack of the hydrogen ions. The colloid-fixing action of small amounts of quinin is an expression of

their lecithin-precipitating quality, while stronger concentrations dissolve lecithin. The extensive paralellism between narcotics and quinin supports the theory that the action of quinin is a cell narcosis.

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**Studies on the Chemotherapy of Silver and Arsenic Compounds in Experimental Tuberculosis.**

*Maurice I. Smith, Am. Rev. Tuberc., 6: 183, May, 1922.*

This is a report of an investigation conducted on the chemotherapy of some arsenic and silver compounds in tuberculosis, the results of which permit the following conclusions: Neo-arsphenamin and silver arsphenamin have a very slight inhibiting action on the growth of the tubercle bacillus in vitro. Colloidal silver oxid has no effect whatever on its growth, while silver methylene-blue has a very considerable inhibiting action on its growth. None of these substances has any demonstrable effect on the pathogenicity of the tubercle bacillus when exposed to their action in vitro at body temperature for 48 hours: nor, when administered to experimentally infected tuberculous guinea-pigs, have they any influence on the course of the disease.

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**An Experimental Investigation of the Supposed Poisonous Qualities of the Granary Weevil, *Calendra Granaria*.**

*Florence Defiel, Am. J. Trop. Med., 2: 199, May, 1922.*

A review of the literature substantiates the current opinion concerning the poisonous nature of *Calendra granaria* and its possession of the properties of cantharidin. Since no experimental work supports this theory, Defiel undertook feeding experiments in which rats, mice, chickens, frogs and a rabbit were used; vesicating experiments with herself as subject in all but a very small number of trials; and subcutaneous inoculations, using rats and mice. The weevils used were separated from the grain, killed by heat, to obviate the possibility of any insecticide entering into the subsequent reactions. They were then dried in a hot chamber at 60° C. until they were sufficiently brittle to be pulverized, and the dry powdered insects were bottled and used when desired to make the various preparations.

The insects were fed to the animals either dry in capsules, moistened to a paste with distilled water, or extracted with distilled water and the clear solution used. In every case control preparations, made from powdered Chinese blister beetles (various species of *Mylabris*), were used under identical conditions. In these ingestion experiments there was no evidence which would justify the opinion that "these weevils have nearly the same medicinal properties as Spanish flies". Solvents employed for the vesicating experiments were alcohol, chloroform, ether, acetic acid, acetic ether, water, clove, cedar and almond oil. The control preparations of true blister beetles were made from various species of *Mylabris* as before. The method of applying the solutions was similar to that employed by Fabre in his experiments on urticating insect larvas, namely that a moisture-proof, air-tight bandage was used. By way of summarizing the experiments on the vesicating power of the granary



weevil, the evidence that they possess no such property is without contradiction so far as the writer's experiments have been carried out. Without exception, the control preparations with Mylabris caused vesication, and since the materials used were the best solvents of cantharidin, it seems to follow that *Calendra granaria* possesses no cantharidin. The subcutaneous inoculation experiments gave similar negative results. It is therefore justifiable to conclude that the granary weevil cannot be used as a substitute for the blister beetle, nor is there any evidence to indicate that it is responsible for cases of poisonous flour.

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**The Calcium Content of the Blood in Guanidin-Poisoning.**

*Gustav Bayer, Ztschr. f. d. ges. exper. Med., 27: 119, Berlin, April 8, 1922.*

Among recent theories of tetanus the best is that of Noel Paton. He found that methyl guanidin was increased in the blood and urine in tetany, and that poisoning with methyl guanidin caused symptoms similar to those of tetany. A striking feature is that the administration of calcium salts, which has a good effect in tetany, has not in guanidin poisoning. As in the latter there was decreased coagulability of blood the author studied the calcium content of the blood of cats, rabbits and guinea pigs poisoned with guanidin. In tetany also an abnormally low calcium content of blood has frequently been found. The calcium content was tested on frogs' hearts, in which perfusion with solutions of low calcium content causes decrease in the height of contraction. Trendelenburg's method was used, and Kahlbaum's guanidin hydrochlorid or methyl guanidin for the intoxication. If a frog's heart was perfused alternately with normal serum and the serum of an animal that had been intoxicated with guanidin, the contraction was lower in the latter case. The decrease in amplitude was 17%, which corresponds to a calcium decrease of 45%. As it is a question of the proportion of calcium to potassium ions the result was still more pronounced on diluting the serum. Therefore guanidin intoxication in animals causes deficiency of calcium ions in the serum in a few hours.

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**The Liver Changes in Mushroom Poisoning.**

*Paul Klemperer, Virchow's Arch. f. path. Anat. etc., 237: 400, Berlin, March 28, 1922.*

The author reports the anatomic examination of the liver in 19 cases which he divides into acute (up to five days' duration) and subacute. Probably all the cases were due to poisoning with *Amanita phalloides*. In the acute cases there were extensive areas of fatty degeneration in the liver, and in addition small areas limited to a few cells or cell groups, where the cells were dead, sometimes also there was regeneration and proliferation of bile ducts. The picture resembles that of phosphorus intoxication, but has nothing to do with that of acute yellow atrophy of the liver. In the subacute cases there were 2 kinds of changes side by side, one consisting of fresh destruction of cells in the center of the



lobules, as in acute atrophy, and the other of reparative and regenerative changes at the periphery of the lobules. A comparison of the 2 groups of cases leads to the conclusion that the cell destruction in the sub-acute cases is not caused by the mushroom toxin directly, but is due to an autolysis, which is a result of the injury of the organ that takes place in the acute stage of the disease. It is perhaps, a disturbance of the glycogen metabolism of the liver similar to that in phosphorus intoxication. Therefore mushroom poisoning does not of itself cause the picture of liver atrophy, but if its course is protracted may cause secondary disturbances which lead to similar changes. If the process finally heals it may give pictures like those of cured atrophy of the liver. It is therefore quite possible that a nodular hyperplasia of the liver may represent a cured case of mushroom poisoning with a protracted course.

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#### Urinary Porphyrin in Lead-Poisoning.

*O. Schumm, Hoppe-Seyler's Ztschr. f. physiol. Chem., 119:139, Berlin, April 20, 1922.*

In lead colic the amount of porphyrin in the urine is found to be increased, though its character has not been determined. In a case of lead-poisoning the diffraction spectrometer showed the exact position of the principal bands of the urine to be 539.0 and 550.0 micromicrons and the secondary to be 573.0 micromicrons. These values do not point to urinary hematoporphyrin, ( $C_{40}H_{86}N_4O_{10}$ ), but agree very well with those of fecal porphyrin ( $C_{36}H_{86}N_4O_8$ ). The latter may be extracted from urine acidified with acetic acid. This was carried out and the substance examined spectroscopically and spectrographically. In a very thin layer it yielded the porphyrin spectrum as well as the urobilin band. Tabulated results show for each band that in the case of ocular determination with the diffraction spectrometer, the values for urinary porphyrin in lead-poisoning were very close to those for fecal porphyrin, but below those for the ordinary urinary hematoporphyrin; in the case of spectrogrammetric determination after exposure with the diffraction spectrograph, the values for urinary porphyrin in lead-poisoning were practically or quite identical with those for fecal porphyrin but, even more than in the first case, below those for urinary hematoporphyrin; in the case of solutions of porphyrin in 0.1 n. KOH, ocular determinations with the diffraction spectrometer showed the values for urinary porphyrin in lead-poisoning to be considerably above those for urinary hematoporphyrin, but, as before, close to those for fecal porphyrin.

In the few cases in which porphyrins have been obtained from urine in the pure state and determined accurately, either a mixture of urinary hematoporphyrin with a small amount of fecal porphyrin, or the former only, was demonstrated. From this it follows that porphyruria in lead-poisoning differs chemically from sulphonal porphyruria and other forms. Generally it seems that in cases of extreme porphyruria chiefly urinary hematoporphyrin is eliminated in the urine while in healthy individuals or in slight porphyruria fecal porphyrin is wholly or predominatingly present.

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**Lead-Poisoning from Impure Flour.**

*M. Gioseffi, Policlinico (Pract. Sect.), 29:656, Rome, May 15, 1922.*

Gioseffi reports several cases occurring in one family, all of whose members showed evident signs of chronic lead-poisoning. After systematic exclusion, as sources of poisoning, of the water supply, the water and wine containers and receptacles, kitchen utensils, etc., the source of intoxication was discovered in the flour from which the family's bread was prepared. Lead had become admixed with the flour during milling of the grain in a house mill having some lead parts. Analysis of the flour revealed actual lead.

The affected persons recovered after treatment with potassium iodid for a number of months, supplemented with warm baths.

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**Method for Microscopic Blood Examination in Lead Workers.**

*Engel, Münch. med. Wchnschr., 69:626, April 28, 1922.*

Schwarz recommended the hanging drop in rapid examination of the blood in lead workers. Seifert recently recommended that the smear should be stained without fixing as this facilitates the examination for basophil granules and net figures. The quantitative determination may be judged in this way. This assumption is doubtful in the light of recent results with lead workers. Basophil granules are found in a larger number in the unfixed preparation. This gives the impression that there are no preformed bodies but that there are basophile substances, as a result of the contraction, which are artefacts and which are not identical with the granules seen after fixing. This makes the examination more difficult. It is possible that this granulation is associated with injury by lead but there must be further experiences and tests before it can be said that the finding is of value.

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**Two Cases of Zinc-Poisoning.**

*R. Engelsmann, Deutsch. med. Wchnschr., 48:488, Berlin, April 14, 1922.*

Warm douches of equal parts zinc chlorid and distilled water 3 times a day were employed in the treatment of a case of recent gonorrhea of the cervix. The patient, in spite of the onset of menstruation, douched 3 more times with the 50% zinc chlorid solution. The next night symptoms appeared, and after two more douches, there were severe abdominal pains, diarrhea, nausea, but no vomiting. The zinc was absorbed by the dilated vessels of the mucous membrane of the uterus. The course was very obstinate, and recovery took two and one-half months. Mercury oxycyanid and silver nitrate can produce the same effects under similar conditions.

The second case occurred in a burner on a dock who was engaged in cutting zinc oxid plate with a blow-torch. The man became dizzy and cyanotic, had cramps, diarrhea, vomiting, and severe meteorism;

the urine contained pus and epithelial cells. Case 1, therefore, was purely resorptive; Case 2 resembled brassfounder's ague, caused through inhalation, the effect of which was partly corrosive and partly resorptive.

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## 1d. BACTERIOLOGY AND PARASITOLOGY.

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**Possible Uses of Quartz Glass and Rock Crystal in the Bacteriologic Laboratory.**

*C. W. Jungeblut, Deutsch. med. Wchnschr., 48:696, Berlin, May 26, 1922.*

The high melting point and resistance to chemical substances and to sudden changes in temperature make quartz glass an important substitute for platinum in the bacteriologic laboratory. Quartz Petri dishes contain no soluble salts that might modify the nutrient medium, in contrast to other kinds of glass. The transparent plates of quartz glass permit inspection of the surface of the medium, but the somewhat more expensive rock crystal glass is preferred for inspection by transmitted light. Other laboratory apparatus can advantageously be made of quartz glass, such as crucibles, spoons and pipets. Quartz loops are inferior to platinum because of deficient pliability but may be used readily in disinfection experiments.

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**On the Differentiation of Various Microorganisms in Culture Mediums with Acetate of Lead.**

*Paolo Pietra, Igiene mod., 15:75, Genoa, March, 1922.*

The glucose or lactose medium with acetate of lead is thus prepared: To 5 c.c. lactose and glucose broth (1%) is added 1-2 drops of acetate of lead (5%) and in the culture tubes thus prepared are placed small tubes of glass upside down to collect the gas that is developed by the action of the microorganisms. In this culture medium are placed the various organisms and the whole placed in the thermostat for twenty to twenty-four hours, after which observation is made to ascertain in which tubes has occurred the blackening and the development of the gas. The experiments of the writer and of other students who have occupied themselves with the question, have demonstrated: (a) for the glucose broth (1) absence of fermentation with or without blackening—in the case of Eberth's bacillus; (2) fermentation without blackening—in the case of paratyphoid A.; (3) fermentation and blackening—in the case of paratyphoid B. (b) For the lactose broth: (1) absence of fermentation with blackening—in the case of Eberth's bacillus and of paratyphoid B.; (2) absence of fermentation and of blackening—in the case of paratyphoid A. The glucose broths give more decided results because they permit the differentiation of all 3 of these organisms

Since the colon bacillus produces gas development and blackening, which identify it in the results with the bacilli of the typhoid and paratyphoid group, it is for this reason not possible experimentally to isolate

it and differentiate it from the various organisms with which it may be mixed. Therefore, although such culture media may sometimes serve in differentiation and diagnosis, it is not possible to advise its use always in substitution for the cultural and serologic methods commonly employed.

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**Transition from Dark to Light Field with the Leitz Mirror Condenser for Dark Field Illumination.**

*Hans Rock, Münch. med. Wchnschr., 69:709, May 12, 1922.*

It is generally impossible to apply the new light-dark field condenser to microscopes of old construction. With these the mirror condenser of Leitz can be used for dark field illumination. It had to be taken out of the optical system, however, when it became necessary to pass suddenly from a dark field to a light field examination. The author has succeeded in making the transition from the dark to the light field without removing the mirror condenser. If, for example, after examining a spirochete specimen, it is desired to examine a gonococcus preparation in a light field, the tube is raised, the spirochete preparation removed, the water on the condenser absorbed with filter paper, the gonococcus preparation put on the stage, a drop of cedar oil put on it and the oil immersion used as usual. The left hand of the observer takes hold of the screw which regulates the distance of the lens from the object, and with careful movements of the screw begins slowly to lower the condenser together with the whole optical system, while looking at the specimen through the eye-piece. Very soon light begins to extend from the edge over the field which was at first completely dark, until finally the whole field is lighted up and the specimen can be sharply focused and examined as usual. The distance from the lower surface of the stage to the upper surface of the condenser in this form of lighting is about 1 to 1.5 cm.

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**A New Simple Device for Ultramicroscopy.**

*V. Vanni, Policlinico (Pract. Sect.), 29:614, Rome, May 8, 1922.*

The author has constructed a new device for the ultra-microscope, which does not require a special condenser, but makes use quite satisfactorily of the ordinary Abbé condenser which does not have to be removed or replaced. The new device entails no immobilization of the microscope, since it may be attached or detached in a moment—being thus simple and easy to use. In place of the iris diaphragm, which has to be kept wide open, there is inserted just beneath the Abbé condenser a small glass slide, on which a rectangular strip of black paper has been so pasted that one of its sides coincides with the base of the slide. Strong rays of light (direct sunlight, arc-light, Nernst lamp, etc.) are made to strike the mirror. For purposes of examination one needs the common achromatic no. 3 objective (Koritska, Reichert, etc.). Any powerful ocular may be used (4 or 5 Huyghens; 8, 12, 18 compensatory), the tube of the microscope being completely pulled out. With this arrangement, by using, say, a no. 4 Huyghens ocular and a no. 3

objective, giving a total magnification of only 95 diameters, one may distinguish—in the form of glistening, oscillating points on a dark field, displaying brownian movements—the most minute particles of colloidal silver, invisible ordinarily with the most powerful immersion lenses. After examination, all that is necessary is to remove the glass slide, and the microscope is ready for routine work.

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**Studies on Cultural Requirements of Bacteria. I.**

*J. Howard Mueller, J. Bacteriol., 7: 309, May, 1922.*

In these studies upon the problem of the nutritional requirements of certain bacteria the plan of the work was to start with meat-infusion peptone broth, to eliminate such factors in its composition as could be managed experimentally, and to substitute known compounds, such as amino-acids, purin bases, etc., or failing in this, to determine, if possible, the chemical nature of the material removed from the media. Types I, II, and IIA of the pneumococci, and a strain of *Streptococcus hemolyticus*, were used. The pneumococcus strains were each passed through 2 mice, the streptococcus through 1 mouse, and stock cultures made from the heart blood of the second mouse were placed in small tubes containing about 1 c.c. sterile human blood. The blood was obtained in the usual way, defibrinated, and incubated twenty-four hours to insure sterility, before being inoculated from the heart blood of the mice. After inoculation the tubes were incubated eight to ten hours until the organisms showed growth and they were then stored in the ice box. For transplanting ordinary meat-infusion peptone broth containing 0.1% glucose and brought to pH 7.4 to 7.8, was used. A small loopful of the blood culture was transferred to the broth, and after incubating 18-24 hours, the culture was used in the case of the pneumococci for the inoculation of a second similar tube of meat-infusion broth. These 2 cultures were known respectively as A and B cultures. Experimental media were inoculated from the B cultures in the case of pneumococci, and from the A tubes with streptococci. In this way it is believed that the food requirements of the bacteria remain constant. The stock cultures remain alive for long periods of time. For the adjustment of experimental media a reaction of pH 7.4-7.8 was used for all the strains of test organisms. For routine work and in all experimental media 0.1% glucose was added since this quantity is insufficient to produce acid in amounts great enough to kill the cultures in 24 hours, or to interfere with agglutination with specific serums. A glucose salt solution used to test the salt requirements of bacteria was composed of: NaCl, 1.0%; MgSO<sub>4</sub>, 0.04%; CaCl<sub>2</sub>, 0.02%; HK<sub>2</sub>PO<sub>4</sub>, 0.2%; glucose, 0.2%; phenol-red, 80 c.c. of 2% solution per liter. All media were sterilized by autoclaving for 10 minutes at 10 lb. pressure.

In preliminary experiments on infusion broth using 3 lots of media it was found that the meat-infusion seemed to contain not only the accessory substances, but also peptones, amino-acids or other sources of available nitrogen. Experiments seem to indicate that 2 classes of organic compounds are required for the growth of pneumococci and streptococci, the first supplied by protein degradation products, the



second by extractives of meat. Both occur together in ordinary meat-infusion, but they may be separated more or less completely in several ways. The necessity for a nonprotein substance is shown most clearly by the failure of a trypsin digest of purified casein to support growth, while that of impure casein is satisfactory. Experiments on the repeated extraction of meat, and chemical fractionation of meat infusion gave further evidence of the presence of 2 classes of compounds in the meat infusion and a possibility of a separation of the 2 classes of compounds were evidenced. The writer states that there is every reason to believe that there may be several individual factors falling into each of these 2 groups.

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## Studies on Cultural Requirements of Bacteria. II.

*J. Howard Mueller, J. Bacteriol., 7: 325, May, 1922.*

In a previous paper of this series the writer intimated that by treating an infusion of beef heart with charcoal, 2 factors necessary to the growth of hemolytic streptococci were removed, and that these factors could be again supplied by the addition of commercial peptone or of a sulphuric hydrolysate of casein to the charcoal-treated infusion. In this paper it is shown that this actually takes place. Certain growth-determining factors were removed from beef-heart infusion by boiling for 25 minutes with 10% norit, wood charcoal. The resultant decolorized infusion is unsuitable for the growth of streptococci while the heart infusion, with glucose-salt solution, constitutes a perfectly satisfactory medium for the strain of streptococcus used, without the addition of peptone. Reactivation of the decolorized infusion was secured with a sulphuric acid hydrolysate of casein. A number of proteins were submitted to  $H_2SO_4$  hydrolysis, and tested with decolorized infusion. The hydrolysates of casein, meat protein, edestin, egg-white, and to a lesser degree, egg-yolk and gelatin, were able to reactivate, while the material from wool, silk and wheat gluten were inactive.

After trying a number of methods for the separation of an active fraction from hydrolyzed casein, with little success, it was finally found that a solution of mercuric sulphate in 5% sulphuric acid would serve to throw down a precipitate containing most, if not all, of the activating material. An actual separation of this material into 2 fractions was demonstrated by purifying the active fraction by fractional precipitation of the first  $HgSO_4$  precipitate by  $HgSO_4$ . This separation was also secured by means of  $Ag_2SO_4$  and baryta. So far as has been learned, known amino-acids will not function in place of either of these fractions. The fractions are called X and Y. The silver sulphate precipitate or X fraction does not depend for its activity on the pigment. It escapes precipitation by phosphotungstic acid under certain conditions, but it is readily destroyed by this reagent. The silver sulphate precipitate, or Y fraction contains a considerable quantity of a new sulphur containing amino-acid, the relation of which to the active Y has not yet been demonstrated.



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**Virulence of a Microörganism and Its Dependence on the Culture Medium.**

*W. F. Harvey and K. R. K. Iyengar, Indian J. M. Res., 9:726, Calcutta, April, 1922.*

The virus used was fowl cholera, and the investigation related to the maintenance or loss of virulence of the organism by weekly subculture on blood agar and on ordinary tryptagar made from mutton. The tryptagar simply had rabbit's blood added to it in the proportion of 10%, while the tryptagar had a reaction of pH 7.4-7.6. The organism at its isolation was found to be extremely virulent to pigeons by intravenous inoculation. That this virulence can be fixed by maintaining serial cultivation on blood agar is shown by trials of virulence on pigeons made at varying periods by intravenous injection throughout the twelve months. The test of virulence of the strain of fowl cholera used proves that when the organism is subcultured weekly on ordinary agar, it is at the end of twelve months only able to kill in a dose of 1 mg., whereas when subcultured on blood agar the virulence is maintained.

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**Experimental Production of Hypersensitiveness in Bacteria.**

*Alfred Schnabel, Deutsch. med. Wchnschr., 48:654, Leipsic, May 19, 1922.*

It is possible to make bacteria hypersensitive to certain substances and especially to those substances against which bacteria can be made resistant. The desired species of bacteria was implanted on equal amounts of a suitable medium containing decreasing amounts of some substance injurious to bacteria. The bacteria growing in the stronger concentrations showed greater sensitiveness than those in the weaker solutions and the controls. The sensitization caused by the different concentrations was manifested in the following manner: Whereas, a control culture of staphylococcus grown in mercury-free medium is inhibited against reducing methylene-blue by a mercuric chlorid concentration of 1:640,000, the inhibitory concentration for a culture grown in bouillon with 1:50,000 bichlorid is 1:1,280,000 (nonspecific decrease of resistance), for a culture made hypersensitive by growing in a nutritive bouillon with a bichlorid content of 1:30,000,000 it is 1:2,560,000, and for a culture grown in bouillon with 1:100,000 bichlorid it is 1:20,000. In the same experiment the limit of inhibitory concentration of phenol used for testing the sensitiveness, with a culture grown in bouillon with mercuric chlorid content of 1:50,000, was 1:800, but for all other cultures grown in bichlorid, as well as for the resistant and the hypersensitive bacteria and those grown in mercury-free bouillon it was 1:400. The phenomena of resistance and hypersensitiveness therefore are manifested only toward the bichlorid used for preliminary treatment and not toward the phenol. The greater sensitiveness of the culture grown in bouillon with 1:50,000 bichlorid toward phenol was also found toward various substances, and is therefore to be interpreted only as a specific decrease of resistance.

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**Studies on Thermophilic Bacteria. I. Aërobic Thermophilic Bacteria from Water.**

*Lethe E. Morrison and Fred W. Tanner, J. Bacteriol., 7:343, May, 1922.*

The thermophilic bacteria are those which grow at temperatures so high as to be fatal to most microorganisms. Since 1879 bacteriologists have studied these bacteria, with varied and interesting results. The writers give in table form an extensive review of the voluminous data on thermophilic microorganisms. The present investigation has been limited to a study of some of the characteristics of 52 cultures of aërobic thermophilic bacteria from water furnished by the Illinois State Water Survey. Many types of water from different sources including deep wells, shallow wells, drilled and dug wells, raw and treated municipal supplies and springs were used. Of 224 samples of water, 60 contained thermophilic bacteria according to the method adopted for their isolation.

Agar plates were poured in the usual way. Later it was found that the agar slants could not withstand the high temperatures, so transfers were kept in broth. With one or two exceptions, the media and technic used in this study were those recommended by the Committee on the Descriptive Chart of the Society of American Bacteriologists. The cultures were all grown at 55° C. Without exception the 52 cultures formed spores and in this characteristic seem to agree with most of the thermophilic bacteria which have been described in the literature. This common characteristic, plus their strong proteolytic ability in connection with their high temperature relations, makes them of importance in food preservation. All the cultures liquefied gelatin at 55° C. With litmus milk, peptonization occurred with at least 75% of the cultures; and in each of these cases the medium was alkaline. None of the cultures fermented any of the sugars, but many of them did produce acid in glucose or sucrose broth; this, together with the fact that all of them showed diastatic action on starch, would seem to indicate that these thermophiles decompose the more complex carbohydrate molecules more readily than they do the simple sugars.

Thermophilic bacteria are widely distributed in nature and since they can live at widely varying ranges of temperature, cause serious losses in those industries where high temperatures are used for controlling bacterial development. This ability of thermophile bacteria to live at high temperatures, may be due, the writers suggest, to a particular property of the protoplasm (water content?). The consensus of opinion seems to be that thermophiles are merely variations of common nonthermophilic microorganisms that have adapted themselves slowly to high temperature. The writers believe that the division made by Bergey into true thermophiles and facultative thermophiles seems to be the most tenable up to the present time.

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**Thermophilic and Strictly Anaërobic Bacteria.**

*R. Veillon, Ann. de l'Inst. Pasteur, 36:422, Paris, May, 1922.*

About 10 tubes, containing a deep layer of glucose-gelose, are  
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heated on the water-bath at 100° C. for 10 to 15 minutes. They are then placed in water at 38°, the medium remaining liquid during the inoculation. By the aid of a pipet drawn out well in the flame, a bit of the material (excrement) is placed in one of the tubes and well mixed, by shaking. The same pipet is then carried into the other tubes, without renewing the inoculation material. The tubes are shaken, but not so thoroughly as with the first tube, and are then plunged in cold water in order to solidify the gelose quickly. In order to isolate thermophilic bacteria, the tubes are placed in the water-bath at 50°, the temperature being then raised to 55° and 58°. Naturally, only thermophilic, or thermotolerant, bacteria can produce colonies after this treatment. Deep cultures from the tubes were made, on glucose-gelose and in parallel series, one at 55°, the other at 37°.

For culture in liquid media, test-tubes and large flasks were used. The latter were required when quantities of 250 to 300 c.c. were employed. The capacity of the flasks was 1 liter. The flasks, tested for heat and pressure, end in a long neck, whose orifice is absolutely sealed with mercury. Gases may thus be removed at will without contaminating the medium, or arresting the culture. The tubes and flasks were inoculated, boiled in a vacuum, rinsed with illuminating gas and closed and sealed in vacuo. Gelatin cultures were also made.

From the excrement examined, the author obtained bacilli of different species. The latter were strictly anaërobic and tolerant of heat. One form was spirogenic. All 3 species developed between 20° and 58°, all coagulate milk, digesting casein more or less. The author terms the bacilli Thermo alpha, T. beta and T. gamma. T. alpha digests cooked albumin. All three ferment sugars, producing acetic, propionic and butyric acids and carbonic acid, hydrogen sulphid and ammonia. Amins are produced, strongly by T. alpha, feebly by T. beta. The bacilli are not pathogenic. The temperature of 58°, at which these bacteria can act, is frequently present in fermenting excrement.

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### **A Cultural Study of Anaërobic Spore-Bearing Bacteria with Strains Isolated by the Barber Single Cell Technic.**

*Morton C. Kahn, J. Med. Research, 43: 155, April-May, 1922.*

The results of observations on 15 anaërobic spore-bearing bacteria of different species, the origin and purity of which had been determined, are here reported. The Barber single cell pipet has proved to be entirely satisfactory for the isolation of organisms in pure culture, and is the most feasible method known. Stock cultures were grown on 0.5% beef infusion agar to which 2% Wolf's casein digest substance was added. Neither animal serum nor carbohydrate was used. The medium was constantly adjusted to pH 7.2, which was found to be the optimal degree of hydrogen-ion concentration. To secure anaërobiosis, the deep-culture methods of Veillon and Zuber were employed. It was found that a layer of paraffin improved the results, but growth was not regularly secured until caps of petrolatum jelly, 1.5 cm. or more in height, were placed on top of the medium, which had previously been boiled for fifteen minutes. This vaselin-seal boiling method was there-

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fore adopted as the most reliable way of obtaining anaërobiosis, especially in liquid media. A Pasteur pipet was used to make transplants and manipulate the organisms.

On the basis of proteolytic reactions, certain of the anaërobes were separated into the 3 groups—strongly proteolytic, feebly proteolytic, and nonproteolytic (or saccharolytic), respectively. The first group contained *B. sporogenes*, *B. botulinus*, *B. oedematis maligni*, and *B. histolyticus*; the second, *B. putrificus*, *B. tetani*, *B. bifermentans*, *B. bellonensis*, and *B. aërofoetidis*; and the third, *B. welchii*, *B. tertius*, *B. fallax*, *Vibrio septique*, and *B. oedematiens*. The presence of fermentable carbohydrates did not affect the proteolytic reactions. In some cases these reactions may be of specific differential value, but in the majority of cases they serve only to distinguish the 3 groups, and differentiation of a species within one of the groups must be made by carbohydrate-fermenting properties of the bacteria.

The morphology of the organisms varied with changes in environment and conditions of cultivation. Even when a constant medium and technic were employed, the morphology of any given organism remained only fairly constant, and in some cases even when all conditions were kept the same, variations were noted. Morphology, therefore, offers but little aid in differentiation. Neither can the bacteria be classified on the shape of the colonies.

The production of hemolysins was studied by the method of Lyall, the bacteria being grown in broth made according to Lyall's formula with the addition of 2% casein digest fluid and anaërobiosis being secured by the vaselin-seal boiling method. It was concluded that hemolytic properties may in some cases be of differential value.

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**Experimental Studies of the Nasopharyngeal Secretions from Influenza Patients. VIII. Further Observations on the Cultural and Morphologic Characters of Bacterium Pneumosintes.**

*Peter K. Olitsky and Frederick L. Gates, J. Exper. Med., 35:813, June 1, 1922.*

*Bacterium pneumosintes*, a minute bacilloid body of regular form, from 0.15 to 0.3 micron long, and with a breadth about  $\frac{1}{2}$  or  $\frac{1}{3}$  its length, which was obtained from nasopharyngeal washings of patients suffering from acute epidemic influenza, has been under cultivation for over three years and has maintained its original morphological and cultural characteristics, when grown in the original medium. Its adaptation to a saprophytic existence has, however, been accompanied by a loss of pathogenicity. The strains now grow readily under strictly anaërobic conditions in a variety of media with peptone broth as a base, enriched with fresh tissue, blood, or by the growth of other bacteria such as the *Bacillus coli*. Surface colonies, also, have been obtained on blood agar plates in an anaërobic jar, these various methods of cultivation being adapted to special purposes. The organism grows in larger forms in broth cultures than in the ascitic fluid-tissue medium, but the serological reactions remain the same, and on transfer to the

original medium the minute forms reappear. Neither freezing nor drying in vacuo have any effect on the bacterium, which probably remains viable for long periods in the dry state.

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### **The Microörganism of Sugar Gum.**

*H. Violle, Ann. de l'Inst. Pasteur, 80: 439, Paris, May, 1922.*

A bacterium, capable of transforming clear and liquid sugar media into viscid and opaline masses may be isolated from vegetable foods containing saccharose, such as dates, figs, sugar-cane, beets, molasses, jellies and syrups. Large quantities of molasses, containing 10% saccharose have been damaged in this manner. The viscid product is called sugar gum. The latter is associated with the presence of small granules, of the size of a pin's head, occurring in contaminated vats. Van Tieghem found bacteria in the granules resembling certain gelatinous algae (nostocs). On account of their color, resemblance to the nostocs and grouping suggestive of intestinal loops, he called the bacterium *Leuconostoc mesenteroides*. The author has made a thorough study of this bacterium.

It is a coccus about the size of an average *Streptococcus lacticus*. It has a capsule of variable size, which disappears in artificial culture media. After 3 or 4 inoculations, the culture assumes fixed characters, containing diplococci having a very fine capsule. The capsule cannot be shown in ascitic-liquid media. It appears to be secreted, in a few minutes, by the bacterium, its nature being ancestral and protective. The coccus is immobile and forms no spores, stains with the Gram and usual basic stains, and the capsule may be shown by double staining. For cultures, gelose, gelatin, gelose with sweetened haricots, carrots or bouillon may be employed. Under favorable conditions, proliferation is active, capsulated forms occur and the medium becomes viscid and opalescent. A temperature of 37° C. produces rapid growth, but the liquid does not become viscid. Viscidity and numerous capsulated forms occur with temperatures of 2° to 8°. Milk is slowly coagulated, but does not become viscid.

The coccus grows well for 2 months on inclined sugar-gelatin at laboratory temperature. Transfers should be made every 2 weeks, or every month. The viscid gum is formed only from saccharose. Ten per cent. sugar yields the maximum viscosity. The viscid substance is precipitated by 95% alcohol. The precipitate, washed in alcohol and redissolved in water, does not reduce Fehling's solution and does not color iodine. Boiled with sulphuric acid, it reduces Fehling's. The coccus does not contain reducing diastases, and is not pathogenic. The gum-forming property is scarcely utilizable, since the more valuable substance, sugar, must be destroyed. However, the total transformation of starch and sugar is avoided in the manufacture of beer. The gum itself has no practical value, for better gums of the sort may be obtained from other bacteria.



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**The Pathogenic Effect of the *Corynebacterium Abortus Infectiosi* of Bang.**

*M. Klimmer and H. Haupt, Deutsch. Arch. f. klin. Med., 139: 33, Leipzig, April 18, 1922.*

The bacillus discovered by Bang and Stribolt in 1897 is a short ovoid form and is easily cultured from the aborted fetus of a cow if there is an O<sub>2</sub> tension below 21% (i. e. that of atmospheric air). Bang's bacillus may be made to grow aërobically if there are frequent stab cultures. The colonies are then as large as a pin-head and tend to be confluent; they are granular, opalescent, glossy and translucent. The bacillus of Bang is pathologic for cows, sheep, mares and goats. It causes an inflammation of the uterine mucosa, which extends to the chorion. It then enters the fetus, where bacteremia results with purulent hemorrhagic gastro-enteritis. It disappears from the genital organs after abortion. Reinfection probably comes from the breast, in which the bacillus remains permanently and is excreted with the milk. The serum of animals which harbor it in their udders contains various antibodies. Infection probably occurs from contaminated food. Inoculation of guinea-pigs with milk containing the bacillus of Bang produces nodules in lymph-glands and internal organs resembling those of tuberculosis. As the bacterial content of this organism in commercial milk is 13% to 32%, this is an important danger for man. Milk products are just as dangerous, as the bacillus is very resistant. Many country women who abort frequently without apparent cause have been closely associated with infected cows. Antibodies were found in the serum of 72 out of 425 children. Diarrhea in calves is a very frequent secondary infection in places where this organism is common. There is considerable serologic, cultural and morphologic similarity between the bacillus of Bang and *Micrococcus mellitensis*. Fever and swelling of the spleen were found in guinea-pigs infected with both organisms.

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**Experimental Infection of the Guinea-Pig with *Bacillus Melitensis* (Bruce) and *Bacillus Abortus* (Bang).**

*R. H. Jaffé, Virchow's Arch. f. path. Anat., etc., 238: 119, Berlin, April 22, 1922.*

These two species of bacteria are so closely related that it is impossible to distinguish definitely between them serologically. Experiments were made to determine whether the undoubted differences in pathogenicity corresponded to differences in the tissue reactions in an animal sensitive to both species. From previous experience it seems that only *B. melitensis* is pathogenic for man. Intratesticular injections in guinea-pigs produced infiltrates made up of large clear cells, largest in 6 to 8 weeks, after the acute inflammatory symptoms had disappeared. These clear cells of roundish oval form were diffusely scattered through the interstitial tissue and also broke into the tubules, or they were collected into definitely circumscribed loose foci. The nucleus present in most of the cells was pale and poor in chromatin and had one or several nucleoli. The protoplasm contained vacuoles and rests



of phagocytized cells; and in younger foci, with suitable staining, bacteria could be demonstrated in the cell bodies. Qualitatively these findings were the same for both species of bacteria, but quantitatively they were more pronounced in infection with *B. abortus*, and this was true of changes in other organs, particularly the spleen, liver and kidneys, which also underwent retrogression more rapidly in infection with *B. melitensis*. In intra-ovarian injection (by laparotomy) there were only slight local reactions in the form of small circumscribed filtrates made up of lymphocytes and a few mononuclear cells which disappeared without injuring the follicles, but there was severe general disease. An animal infected with *B. abortus* died after seventy days of peritonitis following rupture of the spleen. In the exudate there were a few abortus bacilli; in this animal there were also the most pronounced changes in the organs; spleen, liver, kidney and lymph glands were strewn with clear-celled nodules, and in this one case there were slight central necroses. The melitensis animal was killed at the same time. It was very much emaciated and the spleen moderately enlarged. All lymph glands were swollen, but the clear-celled nodules could be demonstrated only in the lymph glands. Serum agglutinated malta bacilli at 1:1280 abortus bacilli at 1:640. Intraperitoneal and subcutaneous injections did not give any further information. The bacteria could be demonstrated in the spleen eighty days after the injection. The differences in the changes caused by these two species of bacteria in the animal body were only in the extent and not in the nature of the filtrate. They were more pronounced after abortus than after melitensis infection. The infiltrations resemble tubercle nodules to a certain extent, but the epithelioid cells of the tubercle are more compact and stain more deeply, and particularly (except in one case) the central necrosis was absent.

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**Some of the Factors Contributing to Toxicity of Botulinus Toxin by Mouth.**

*Jacques Bronfenbrenner and M. J. Schlesinger, J. A. M. A., 78: 1519, May 20, 1922.*

Botulinus toxin is a poisonous substance elaborated by *Bacillus botulinus* and quite analogous to the toxins produced by *B. diphtheriae* and *B. tetani* in all the essential properties identifying it as a true bacterial toxin. It may be isolated from cultures by filtration. It kills experimental animals in small doses with symptoms characteristic of the disease. It is thermolabile and is neutralized by a specific type anti-toxin. Symptoms of poisoning appear after a characteristic incubation period, but this period is appreciably shorter than in the case of either tetanus or diphtheria toxin. Botulinus toxin, however, differs from the latter two toxins in that it is toxic by mouth in very minute amounts. In view of the relative instability of botulinus toxin in mildly alkaline reaction and its marked resistance to acid reaction, it seems likely that it is in the main absorbed from that part of the digestive tract which is acid in reaction, namely, the stomach and upper duodenum.

This toxin also differs from other bacterial toxins in that precipitation with ethyl alcohol practically destroys it, as proven in recent out-

breaks of food poisoning where some of those who escaped severe poisoning had partaken rather freely of alcoholic beverages during the meal. This was also proven by experiments. The amount of food present in the stomach will serve to diminish this protective effect of alcohol.

Botulinus toxin is capable of an extraordinary increase in potency when it encounters the condition of hydrogen-ion concentration similar to that present in the stomach during active digestion. This increase in potency is so marked that were only an infinitesimal quantity of the acidified toxin absorbed into the general circulation, it would be sufficient to kill the animal. Most recent results indicate that probably all batches of toxin may be increased in potency if proper conditions of acidification, time and temperature are found for each.

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**Search for Diphtheria Bacilli in the Urine of Diphtheritics.**

*Erodiade Petriccioni, Ann. d'igiene, 32:212, Rome, March, 1922.*

From among the urines of 20 diphtheria patients examined, typical and virulent diphtheria bacilli have been isolated in only 1 case, so that this method of diffusion of the diphtheria bacillus has only a relative value from a prophylactic point of view.

Diphtheroids have been encountered more frequently, the prevailing type being that of Hoffmann; thus, morphologically, by the absence of granules and absence of sugar fermentation, differentiation from the true diphtheria bacillus is rather easy. However, these urines frequently show types of pseudodiphtheria bacilli very closely similar to the true diphtheria bacillus, and easily confused with the latter if examination is limited to smears and cultures. Attempts at differentiation must thus include fermentation tests on the various sugars, and biologic tests must never be omitted in cases where the microorganisms isolated from the urine show polar granules.

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**Behavior of Diphtheria and Pseudodiphtheria Bacilli in Bile (in Culture and in the Body).**

*Guido Rigobello, Ann. d'igiene, 32:208, Rome, March, 1922.*

The author has attempted to determine whether bile (which for some microorganisms represents an optimum culture while for others it is distinctly bactericidal) could enhance the development of the diphtheria bacillus when added to the ordinary forms of Loeffler's medium. Inoculations of undiluted bile with diphtheria bacilli proved that the biliary secretion is bactericidal; when present only in moderate proportions, to about 15%, bile allows growth of the microorganism, although to a very limited extent; the growth of the bacillus in the same media, without the addition of bile, was unaffected. These results may be interpreted as denoting that, in minute quantities and greatly diluted, the biliary acids do not exert any bactericidal action, any tendency to such action being offset by the alkalinity of the bile which rather favors bacterial growth, and by the traces of cholesterin present

which, from its nature as a lipoid, may act as an adjuvant to such growth.

The pseudodiphtheria bacillus of Hoffmann survives even in the presence of a 40% bile concentration in glycerin broth. The bacillus of xerosis continues to grow in a concentration of bile of over 50% in glycerin broth. Thus, at a concentration above 20%, there occurs no growth of diphtheria bacilli, while the pseudodiphtheria bacilli continue to grow luxuriously, a fact which could be utilized for the later differentiation of the 2 groups of microorganisms.

It was then attempted to discover experimentally whether the diphtheria bacillus could find within the gall-bladder a suitable habitat, by inoculating animals in the usual manner subcutaneously, peritoneally, or directly into the gall-bladder. In the bile of animals killed during infection, or dead in the course of the experiments, it was impossible to demonstrate the presence of diphtheria bacilli either by smears, cultures, or animal inoculations. No macroscopic or histologic lesions could be detected. Death could be attributed only to the toxins contained in the microorganisms introduced into the circulation or to toxins produced locally by lysis of bacteria. Therefore, bile does not affect the production of toxins and does not modify the latter's deleterious properties, but is distinctly bactericidal for the microorganism.

These findings justify the conclusion that, just as in animals inoculated experimentally by the usual routes, the diphtheria bacillus could not be found in the gall-bladder, so by analogy, the human gall-bladder cannot be the seat of bacterial growth in human diphtheria infection.

The positive findings of diphtheria bacilli in the gall-bladder could be explained only on the hypothesis that such microorganisms had passed from the circulation into the gall-bladder immediately before death in consequence of some cellular degenerations, commonly occurring as autolytic processes in the cadaver, and that, besides, the bacilli had not yet undergone the bacteriolytic effects of the bile.

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#### **Experiments on Acidity Conditions in the Growth of *Bacillus Macerans* and on the Course of Starch Cleavage.**

*H. von Euler and O. Svanberg, Biochem. Ztschr., 128: 323, Berlin, March 28, 1922.*

*Bacillus macerans* was cultivated in nutrient mediums composed of 100 gm. potato starch, 2 liters water, 2 gm. ammonium phosphate, 0.5 gm. magnesium phosphate and 0.5 gm. sodium chlorid. A part of the medium received only 50 gm. potato starch in 2 liters of this nutrient solution (medium A). Displacement of hydrogen-ion concentration by the activity of the bacillus appears to be very slight. Acidity was estimated in 10 c.c. of medium A and in 5 c.c. 0.3 mol phosphate mixture. The phosphate mixtures had the following composition and gave the nutrient medium the respective pH values:

	A	B	C	D
primary:	5 c.c.	4 c.c.	1 c.c.	5 c.c.
secondary:		1 c.c.	4 c.c.	
pH:	5.2	6.4	7.0	8.3

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The experimental flasks were inoculated with a platinum loop and were kept at 36° C. Optimum growth occurred at pH 6.8. Cell numbers were determined directly under microscope, three days after inoculation. A number of Erlenmeyer flasks containing 100 c.c. nutrient medium (A) were inoculated with platinum loops and the course of starch cleavage studied. Results are summarized in a table from which it appears that starch was split into amyloses almost quantitatively by *B. macerans*. The iodine reaction disappears, total carbohydrate content remains unaltered and the fermentation reaction is negligible as compared to depolymerization of starch.

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**Contribution to the Microbiologic Diagnosis of Malignant Edema.**

*Pietro Betteri, Igiene mod., 15:65, Genoa, March, 1922.*

A case of cow-pox coming to death offered opportunity to the writer to establish the differential bacteriologic diagnosis of the bacillus of malignant edema from other similar microbes. The bacillus of Ghon-Sachs is differentiated from that of malignant edema in that it does not blacken the brain preparation of Hibler. The bacillus of Novy and the bacillus XI of Hibler behave toward the brain preparation just as does that of Ghon-Sachs, i. e. without any tendency to the formation of flagella. Milk coagulates very slowly, without the coagulum separating. The bacillus of Liborius is represented morphologically by a rather large rod-shaped microbe whose flagella have an evident ectoplasmatic extremity, and which is much less pathogenic than the vibrio of Koch. The morphologic quality and biologic nature that differentiate the vibrio septique are, on the contrary, based on the following facts: A motile, slender, detached rod either with short flagella, or sometimes with boat-shaped spores or even with extremities ending in ratchets. They grow on mediums excluded from air and oxygen. On agar they form open colonies, and have fringed borders. They blacken the brain preparation of Hibler. They coagulate milk with subsequent peptonization of the coagulum.

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**The Chemism of Toxin Formation by Bacillus Phlegmonis Emphysematosae, Fraenkel.**

*Katzumi Kojima, Biochem. Ztschr., 128:519, Berlin, March 28, 1922.*

The microorganisms causing gas gangrene have been divided hitherto into 3 main classes, namely Fraenkel's bacillus, the bacillus of malignant edema and the bacillus of symptomatic anthrax. Only when Ficker and Klose had prepared the edema toxin and a true anti-toxin had been obtained from it, strict differentiation of the edema bacilli was undertaken. Two poisons are said to occur with Fraenkel's bacillus, one acting acutely and against which immunization is not possible (Klose, von Wassermann), and a true toxin against which immunization is possible and which is thermolabile (Bull, Britchett). In checking up these findings Fraenkel's species were cultivated on 2%

glucose agar, and a filtrate was prepared and injected into a mouse. Further, Fraenkel's toxin was tested against sheep edema antitoxin and normal sheep serum. Results showed that *Bacillus phlegmonis emphysematosae* has no relation to the edema bacillus. It was found that Fraenkel's bacillus possesses 2 different poisons, a true one that kills after a certain period of incubation, and an acute one which kills immediately. The production of these 2 poisons depends chiefly on the sugar content of the nutrient medium. If the latter contains much carbohydrate, the acute poison is formed and if small amounts of sugar are added the true toxin is obtained. With a small sugar content, growth is not inhibited by the addition of fresh pieces of muscle. The limit of the sugar content with which a true or an acute poison is formed is found fairly constantly at 0.5% glucose, with slight variations. In the medium containing more than 0.5% sugar only the acute poison is usually found, while a true toxin is always detectable in the medium containing less sugar. The true toxin is thermolabile and not dialyzable but may be neutralized with Fraenkel serum. On the other hand the acute poison is thermostabile and cannot be neutralized with immune serum or normal serum. By means of dialysis it is possible to separate the 2 poisons. While the true toxin is retained within the dialyzing membrane without losing its toxin content, the acute poison may be detected in the external liquid by a suitable method. As regards the behavior of hemolysin, the production of the specific hemolysin is very closely related to the true toxin.

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### **The Structure and Mode of Development of Tubercle Bacillus.**

*A. Kirchensteins; Ann. de l'Inst. Pasteur, 36:416, Paris, May, 1922.*

Besides the polar granulations which have been described, tubercle bacilli contain other granular matter situated toward the edges or within the plasma. For showing the structure and development, the author uses the following technic: Young bacilli must be employed, preferably obtained from tuberculous sputum. A particle of sputum is mixed with 1 drop of a 2% solution potassium ferrocyanid. The mixture is spread between 2 cover-glasses in a very thin and uniform film, which is dried in the air and washed in water to remove the ferrocyanid, then stained with boiling carbol-fuchsin and well washed. After application of a differential stain, the film is decolorized with a solution of 2.5-3 gm. sublimed iodine and 1.25-1.50 gm. KI in 100 c.c. 80% alcohol. It is then treated for a few minutes with picric acid solution, made by diluting 1 part saturated solution with 20 parts water. The iodine solution is again applied for 1 or 2 seconds, the film is washed, treated again for 2 or 3 seconds with the picric acid solution, well washed and dried in the air for study. Another method may also be employed: The film is prepared as before, treated for 30 to 40 seconds with 5% solution chromic acid, well washed, and heated to boiling with Delafield's hematoxylin solution. After washing, it is stained with carbol-fuchsin and a differential stain as in the first method.

The bacilli appear as slender rods containing the granules mentioned.  
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tioned, situated on opposite borders, and connected by delicate filaments. These granules unite to form the larger masses commonly observed after the ordinary staining. The author's method prevents the union and shows the granules in their original form. They constitute bacillary nuclei, or similar structures. Before the bacillus divides, a small nucleus appears near the cellular wall. A fine filament connects it with a second nucleus. The first nucleus and filament divide, forming a sort of triangle within the bacillus. The second nucleus, and finally the bacillus, divide. The author has observed short, young bacilli containing 2 nuclei at one end, which form the polar nuclei. This process may also be noted in sporogenic bacteria. The granules may thus produce new bacilli, whether included in, or liberated from, the bacilli. This fact has caused them to be regarded as spores. However, they are neither spores, nor decomposition or degeneration products. An illustrative plate is included.

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**Simple Method for Demonstrating Tubercle Bacilli in Poor Specimens of Sputum.**

*N. Pane, Riforma med., 38:313, Naples, April 3, 1922.*

By some of the newer methods of preparation of sputum for the demonstration of the tubercle bacillus many of the younger forms of bacteria are dissolved, while a large number are affected as to staining properties. Pane describes a method of his own, said to be rapid, and to cause a grouping together of the scattered bacilli in the specimen, without destroying any of them.

The suspected sputum is placed in a sterile glass container, and mixed with 4 times its volume of sterile physiologic saline solution, after which it is placed in the incubator for twenty-four hours, at 37° C. During this period the mucus and cells are dissolved by the proteolytic enzymes set free by the secondary microorganisms which more or less abound in every specimen of sputum. When the specimen is centrifuged, the bacteria alone are thrown down, the other solid organic bodies which usually obscure the field having been done away with; the sediment is then stained according to one of the usual methods (of which the best is the Ziehl-Nielsen). In some cases there were found isolated groups of tubercle bacilli closely bunched together (agglutinated). The author interprets such findings as evidence of a specific defensive immunity on the part of the organism, however slight.

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**The Apparent Increase of Tubercle Bacilli in Incubated Sputum (Bezançon, Mathieu and Philibert's Process).**

*S. I. de Jong and P. Hillemand, Bull. & mém. Soc. méd. d. hôp. de Paris, 38:828, June 1, 1922.*

Sputum (5-10 c.c.) is incubated for 4 days in a test-tube. The sediment at the bottom of the tube then contains a much greater quantity of bacilli than the upper layers. If the direct examination of the deposit gives negative results, 2 c.c. of the lowest layer may be sub-



jected to homogenization. The sputum of 68 patients was examined directly and after incubation. In 87.7% of these cases there was a marked increase and in 10.3% a decrease in the number of bacilli found after incubation. The few cases where a decrease had been noted were subjected a second time to the same comparative test, which then showed generally an important increase of the bacilli after incubation. It can therefore be concluded that a concentration of the bacilli takes place practically always when a sputum containing bacilli is incubated.

The results obtained by homogenization and by incubation alone were compared in 20 patients whose sputum had proved negative by the ordinary direct method of examination. In every case where homogenization gave positive results, bacilli were also found by incubation; 4 were negative by homogenization but positive after incubation; 2 which were negative by both methods gave positive results after homogenization of the sediment obtained by incubation. It is noted that the bacilli found after incubation are granular and grouped into clumps. The incubation method simplifies greatly the technic of sputum examinations and increases markedly its sensitiveness.

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#### **New Methods for Demonstrating the Tubercle Bacillus in the Urine.**

*Giuseppe Fragale, Policlinico (Pract. Sect.), 29: 511, Rome, April 17, 1922.*

In view of the importance and the frequent difficulty of demonstrating the tubercle bacillus in the urine, the author has attempted to devise new methods of procedure of greater ease and certainty of diagnosis. For the purpose of discovering even the smallest number of tubercle bacilli present in a specimen of urine, where such discovery would be totally impossible by any of the other methods, it is best to subject the specimen of urine to a process of mechanical precipitation by means of some colloidal substance, then successively to dissolve and centrifuge the precipitate until a very minute amount of sediment is left for examination. For simple microscopic demonstration of the bacilli it is sufficient usually to add a little liquid albumin and then cause rapid coagulation by boiling, dissolving the precipitate with sodium hydroxid, and centrifuging.

On the other hand, when it is necessary to produce biologic evidence of the disease (cultures, animal inoculations), it is preferable to resort to Ficker's technic for demonstrating the typhoid bacillus. Where cultures are needed, the sediment obtained by Ficker's method is treated according to the method advocated by Petroff for tuberculous sputum. The aim of the newer methods is to eliminate as far as possible the necessity of resorting to biologic tests, which require as a rule at least two weeks. But since by the use of such sensitive tests there may enter an element of doubt due to the great difficulty of distinguishing microscopically the tubercle bacillus from other similar acid-fast bacteria, frequently to be met with along the genito-urinary tract, the following points are to be noted:

When microscopic examination reveals numerous bacterial elements  
(Sec. 1—Page 130)

giving the typical acid-fast reaction and the other properties of the Koch bacillus, any possibility of accidental inoculation of the urine may be excluded and a positive microscopic diagnosis of tuberculosis made.

When the Koch bacillus, in spite of the use of the method described, appears only in a few of several specimens prepared, or only in a few of a number of microscopic fields examined, then, if the urine has been obtained by catheterization under strictly aseptic conditions, with proper sterilization of the external genitals, the microscopic report may be unreservedly positive for tuberculosis. If, however, in addition to the scant number of bacilli there is doubt as to the conditions of asepsis under which the specimen of urine has been collected, the requirements for accuracy of diagnosis demand control and confirmation of the microscopic findings by means of biologic tests, and only cultures or animal inoculations can yield absolute evidence as to the specificity of the microorganism in question.

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**Comparative Tests on the Resistance of Tubercle Bacilli and Related Organisms to Decolorizers.**

*H. Schlossberger, Beitr. z. Klin. d. Tuberk., 50: 144, Jubilee Number, Berlin, March 15, 1922.*

Forty different varieties of acid-fast strains were used in the tests; they included the butyric bacillus, timothy bacillus, Petruschky's milk bacillus (including strains that had undergone as many as 5 successive guinea-pig passages), several bovine and human strains of tubercle bacilli, Friedmann's bacillus, frog and snake tubercle bacilli, and avian tubercle bacilli, some strains of which had been passed through guinea-pigs.

Smears of the different strains were stained with steaming carbol-fuchsin. For differentiation various dilutions of hydrochloric acid were employed, namely 0.05%, 0.25%, 1%, 5% and 20%; also 70% and 96% alcohol, and varying strengths of aqueous solution of sodium sulphite (0.25%, 1%, 10%, 20%, 26%) and of borax (0.2%, 1%, 5%). The decolorizing effects of these solutions upon the stained smear were tested for varying periods of exposure. Aqueous solutions of methylene-blue or of malachite-green were used as counterstains. One series of slides, serving as a sort of control smears, were placed directly into saturated aqueous solutions of anilin dyes (methylene-blue, malachite-green, thionin, Bismarck brown) without previous decolorization, for varying periods.

A distinct difference was apparent between pathogenic and saprophytic strains; generally, the saprophytic strains were more labile. Remarkably, the resistance of the several acid-fast bacteria to the decolorizing action of various differentiating agents did not run parallel. In simultaneous tests of 3 human strains with the same differentiating agent, graphic differences in resistance to the differentiating substance were observed. Passage strains became more resistant to hydrochloric acid than the primary cultures; nevertheless, they did not reacquire all the characteristics of the original strains of tubercle bacilli but essential differences persisted, particularly in their behavior to sodium sulphite.

There is undoubtedly a certain relation between pathogenicity for

warm-blooded animals (guinea-pigs) and acid-fastness, as well as between the degree of resistance to acid and sodium sulphite on the one hand, and the length of time during which a strain has lived and multiplied in a warm-blooded host on the other. The nature of acid-fastness is still an open question. The purely physical explanation on the basis of lipoid substances meets objection because even long-continued extraction fails to eliminate acid-fastness completely. At the same time, the dyes that are insoluble in fats (fuchsin, methylene-blue, eosin) stain the tubercle bacillus relatively quickly and intensely. The differences in the degree of acid-fastness cannot be explained. The more acid-fast tubercle bacilli form a lipoid that stains with Sudan only when grown on medium containing glycerin, while the saprophytes produce it when grown on ordinary sugar. Hence it can hardly be claimed that the acid-fastness of the tubercle bacillus is due solely to its waxy sheath. It is far more probable that the structure and composition of the protoplasm represent the main causes of resistance of acid-fast bacteria to differentiating agents.

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**The Bacteriology of Friedmann's Turtle Tubercle Bacillus.**

*Xavier Cieszynski, Polska gaz. lek., 1:429, Cracow, May 21, 1922.*

Friedmann first thought his strain of turtle tubercle bacillus was a greatly attenuated human strain. But others are convinced that these bacilli can produce tuberculous changes in warm-blooded animals and that they are not harmless. Later Friedmann succeeded in making a preparation from turtle bacilli which after repeated inoculations lost its toxicity even for turtles. This led Müller to admit (with reference to the possibility of attenuation of tubercle bacilli) that the human bacillus may have been a progenitor of Friedmann's bacillus. It remained to determine the relationship of Friedmann's bacillus to the acid-fast bacilli. Guinea-pigs were vaccinated with acid-fast bacilli and the resulting nodules transferred to other animals. While the first injection produced only local tubercles, repeated injections caused severe specific changes even in distant organs. Bacteria from these organs grew like bacteria from warm-blooded animals, indicating that acid-fast bacilli are injurious to warm-blooded animals also. However, Friedmann holds that they are not, interpreting the nodule formation as a "foreign body tubercle" in which Lubarsch and others found giant cells. Lang showed that acid-fast "tubular bacilli" of the turtle when injected into guinea-pigs become disseminated throughout the body but do not propagate; their vitality did not increase after 44 weeks. These bacilli do not cause hypersensitiveness to old tuberculin, but they protect against infection by true bacilli. As in numerous experiments Friedmann's bacilli proved harmless to warm-blooded animals, Lang assumes that they are more closely related to the bacilli of cold-blooded animals than to true tubercle bacilli. Friedmann's bacilli when grown from the first culture at 37° C. looked very much like the tubercle bacilli of warm-blooded animals, and after several inoculations on glycerin agar they could not be distinguished from the latter; morphologically they were more like the bovine than the human type.

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**A Note on the Methods of Cultivating the Gonococcus.**

*Charu Chandra Bose, Calcutta M. J., 16:367, April, 1922.*

Bose finds the following method very satisfactory for primary cultures. About 5 c.c. blood is drawn from the patient (unless a donor is at hand) and defibrinated. About 0.75 c.c. of this is added with a capillary pipette to each of a set of test tubes containing 5 c.c. melted agar (2% and neutral to phenolphthalein) at 55° C. The blood is stirred through with the tip of the pipette and slanted. These tubes are incubated for twenty-four hours. With ordinary care all the tubes come out sterile. The pus obtained from inside the urethra, after swabbing out the glans thoroughly with a piece of cotton soaked in alcohol, is smeared on one or two of the blood agar tubes prepared on the previous day. The rest of the tubes are stored for purposes of subculture in a stoppered jar, the inside of which has been swabbed with mercuric chlorid solution 1-1000, and a little of this solution is left at the bottom. The cotton plugs are covered with filter paper impregnated with the same solution, as agar tubes so kept do not dry quickly and are not so readily invaded with fungi. For securing a carbon dioxid atmosphere, some bicarbonate of soda is placed at one side of a wide-mouthed glass-stoppered jar, and this side of the jar is tilted up by placing a glass rod under it. The inoculated tubes are next put in a beaker and placed inside the jar, the cotton plugs being covered with filter paper impregnated with mercuric chlorid. Some dilute sulphuric acid is next carefully put in by means of a funnel, and this accumulates at the opposite angle of the jar. The glass rod under the jar is then removed and the acid allowed to come in contact with the carbonate. Brisk effervescence sets in. As soon as this has gone half way, the stopper is gently put in, and when effervescence is nearly completed, the stopper is pushed home and ringed with vaselin to secure effective sealing. By this method a growth is secured in twenty-four hours. The colonies have a grayish color, and are moist and somewhat sticky. Smears show the familiar Gram negative diplococci. Sugar tests are made after adding some blood serum to the various sugar media. This method provides a handy medium and does not require elaborate technic. Successful primary cultures are obtained in a large percentage of cases. The blood of gonorrhea patients does not seem to inhibit the growth of the microörganism. The disadvantage of this medium is that, since it is opaque, it is somewhat difficult to isolate the gonococci from chronic cases, where secondary organisms play a large rôle.

Lately Bose has used hydrocele agar (15%) in place of whole blood agar with good results, but one is not always sure of the sterility of the fluid. However, this medium is likely to be of use in vaccine work, where a large yield is necessary. With carefully collected hydrocele fluid 100 tubes can be easily prepared with little loss by way of infection. The gonococci grow on it either with or without carbon dioxid, but the yield with an atmosphere of the latter is far greater.

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**The Serologic Grouping of Meningococcus Strains Isolated in New York City in 1921 and 1922.**

*Alice C. Evans, Pub. Health Rep. (U. S. P. H. S.), 37:1247, May 26, 1922.*

A collection of meningococcus strains made in 1921 and 1922 has been studied in respect to tropin and agglutinin relationships. A strain was assigned to a given tropin group when a suspension of a density equivalent to 5000 parts per million (silica standard) absorbed tropins from the group serum as completely as the homologous antigen of the same density. Strains placed in Group Z were an exception to that rule for they absorb partially from 1, 2, 3 or all 4 of the other groups but fail to absorb sufficient tropins from any one of the well-defined groups to be classified in them. The strains in the 1918-1919 collection were isolated in widely separated parts of the U. S. and a few strains from England were included. There was no apparent correlation between serologic types and geographic distribution. The 1921-1922 strains were all from New York City, and all were isolated from the spinal fluid in cases of meningitis. Among the 1918-1919 strains it was a rare occurrence to find one which did not belong to some one of the well-defined groups, while the majority of strains thus far received in 1922 belong to the generalized Group Z, or show no relation whatever to the definite tropin groups. The 1921 strains are intermediary between the 1918-1919 and the 1922 strains as regards their tropin affinities. The serologic transition in meningococci is even more striking when their agglutinin relationships are considered. There is a marked decrease in the percentage of strains belonging to Types I, II and III, a slight increase in the percentage of Type IV strains and a remarkable increase in the percentage of strains which show no relationship to the 4 types. When tested against polyvalent horse serum such as is used in treatment of meningitis, a much larger percentage of strains was agglutinated than would be indicated by the 1922 agglutination results. A possible explanation of this discrepancy may be the presence of "group" agglutinins in the polyvalent horse serum. It has not yet been determined whether new well-defined types may appear in the strains being isolated at the present time but the impression is that the new strains are indefinite and generalized in their serologic relationships, hence the increase in Type IV strains deserves comment, for this increase along with the increase in percentage of tropin Group Z strains and of strains showing no relationship with the definite tropin groups gives further reason for considering Type IV of a somewhat different nature than Types I, II and III. The number of strains in the 1921-1922 collections is rather small to permit of conclusions but the serologic differences are so striking that they may represent a general transition in meningococci.

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**How Should Meningococcus Material Be Handled in Bacteriologic Institutes?**

*Hundeshagen, Münch. med. Wchnschr., 69:627, April 28, 1922.*

It is important to deny the sensitiveness of the meningococci to  
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cold. Lingelsheim showed that meningococci were not killed by a temperature of 20° C. below zero. There was also a wrong conception of the effect of cold on carriers and the military surgeons often asked for warm cabinets if the carriers were to be transported for a long distance. There is a difference between meningococci which can have suitable culture medium for development at the proper temperature such as those in spinal fluid or such as were immediately transferred to ascites agar or bouillon and the meningococci taken up with cotton plugs and sent for some distance for examination. The first require incubator temperature while the bacteria may be injured by drying in the second instance, and this may result in destruction of the organisms. The cotton plugs kept at incubator temperature seldom gave positive results while smears which were kept in ice-cold cases for hours gave a positive culture in more than 50% of the cases. It is wiser to send smears from the throat on cotton swabs not in warm cases but in air-tight containers, and at a low temperature. Rapid transport is the most important factor.

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**The Demonstration of the Capsules of the Pneumococcus by a Modification of Benian's Relief Stain.**

*R. H. Malone, Indian J. M. Res., 9:804, Calcutta, April, 1922.*

Make a thin smear of the material to be examined, fix by heat, and allow to cool. Pour a few drops of 2% aqueous Congo-red over the slide, stain for about one minute, drain off the excess of stain, and allow the film to dry in air. Treat the film, when dry, with 1% HCl in 96% alcohol for a few seconds. Allow to dry in air. Counterstain with 0.5% aqueous methyl-violet for about one minute. Wash off excess of stain with tap water. Blot or allow to dry in air. Examine with the oil-immersion lens. Before treatment with acid alcohol the organisms are seen poorly, as red cocci surrounded by a faintly stained (pink) capsule on a red background. After treatment the background becomes blue, the organisms themselves appearing as pale blue, shadowy figures. To bring out the organisms clearly, a method of counter-staining is used. Of the common stains, the writer has found methyl-violet and gentian-violet to be the most satisfactory. Methylene-blue stains the organisms rather poorly. The value of the method lies in its simplicity and the absolute certainty with which capsules can be demonstrated.

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**The Peptase, Lipase and Invertase of Hemolytic Streptococcus.**

*Franklin A. Stevens and Randolph West, J. Exper. Med., 35:823, June 1, 1922.*

The enzymes obtained from different bacteria show differences in resistance to heat and in peptolytic and sugar-splitting power. On this account the peptase, lipase, and invertase of hemolytic streptococci were studied for comparison with similar enzymes of other bacteria in the hope that eventually differences would be found sufficient to account for variations in the pathogenicity of different strains of this organism. The method employed to extract the enzymes from the streptococci was



a combination of procedures described by other investigators, with certain modifications, such as the use of phosphate mixtures during grinding and sterilization of the cultures to prevent deterioration of the enzymes, which proved to be exceedingly susceptible to heat, acid, and antiseptics. It was found that the enzymes resemble those obtained from the pneumococcus by Avery and Cullen, and it appears likely that similar enzymes exist in other bacteria. It was determined that the peptolytic enzyme is active between pH 4.4 and 8.7 with an optimum action at pH 7.2, is destroyed in neutral phosphate solution at a temperature of 57° C. continued for ten minutes, and at pH 5.0 deteriorates slowly at 37° C. It is exceedingly susceptible to chloroform, and its action is inhibited by dilutions of gentian-violet. Casein is attacked, but serum-albumin is not digested after three days at 37° C.

The invertase is active between pH 5.0 and 8.0 with an optimum at pH 7.0. It is destroyed by a temperature of 52° C. continued for 10 minutes at an acid concentration of pH 7.0, or after 6 hours at 37° C. at pH 5.0; at this acidity it is more susceptible to heat than the peptase. The lipase is active above pH 5.6, the greatest activity being observed at pH 7.9. It is completely destroyed after heating to temperatures over 55° C. for 10 minutes, and resembles the invertase in its susceptibility to acid.

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**A Peculiar Failure of Hemolytic Action in a Strain of Hemolytic Streptococcus.**

*Eugenia Valentine, J. Infect. Dis., 30:610, June, 1922.*

During titrations by the tube method of the hemolytic capacity of a series of streptococcus cultures belonging to the beta hemolytic group, a peculiar absence of hemolysis was observed in one culture. With this strain (W 12), 0.5 c.c. of an 18-hour broth culture failed to give hemolysis when mixed with 1 c.c. of 5% washed red cells, while 0.4 c.c. of the culture to which 0.1 c.c. of sterile broth was added gave almost complete hemolysis. The phenomenon was not observed in 25 other strains. This failure of the strain to take red cells without the addition of sterile broth indicates a possible source of error in testing hemolytic activity by the usual tube method. In further experiments the phenomenon was markedly constant, except that it was found that a culture of the strain which had been incubated for only six hours caused hemolysis without the addition of fresh broth, while older cultures did not. It appeared probable, therefore, that the failure of hemolysis was due to cessation of growth, and that return of hemolytic activity followed renewed multiplication after the addition of fresh broth. No reason why this particular culture should present this phenomenon was discovered.

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**A Further Inquiry into the Source of the Virus in Blackhead of Turkeys, together with Observations on the Administration of Ipecac and of Sulphur.**

*Ernest Edward Tyzzer and Marshal Fabyan, J. Exper. Med., 35:791, June 1, 1922.*

The authors have continued their studies on blackhead in turkeys,  
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attempting to determine the source of the virus, and the efficacy of certain drugs in the prevention or treatment of the infection. They conclude that the most important source of the virus in the natural transmission of the disease is the intestinal worm, *Heterakis papillosa*, and that measures designed to eliminate this parasite offer the greatest hope of controlling the disease, although confirmatory morphologic evidence of this has not been obtained. Blackhead can be produced in turkeys by feeding large amounts of the virus alone, as obtained from liver lesions, but this artificial procedure is not duplicated in nature. The disease can be constantly produced by contamination of the food of young turkeys with dirt taken from hen yards. Blackhead infection in common fowl is believed to be identical with that of turkeys. Under experimental conditions a large proportion of the *Heterakis* ova fail to hatch out in the intestine, but it is possible that after passing through they may later be taken up with contaminated food.

Powdered ipecac, like other drugs previously tested, is of no practical value in the control of the disease. Its daily administration to the limit of tolerance failed to prevent infection or a fatal outcome in the naturally acquired disease. It may, however, delay the onset of the infection, perhaps because of some physiologic property. Sulphur, also, possibly on account of its evacuant action, tends to delay infection. Recovery from inoculated blackhead is associated with a degree of immunity, but this is not permanent. The fact that blackhead sometimes appears in mature turkeys that have been kept constantly on infested ground suggests that these birds may suffer from repeated attacks.

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**A Method for Counting the Number of Fungi in the Soil.**

*Selman A. Waksman, J. Bacteriol., 7: 339, May, 1922.*

In the ordinary plate method of counting the numbers of fungi in the soil, bacterial growth is so great that the development of fungi is prevented. To obviate this difficulty, use was made of the fact that fungi can grow readily at a much higher acidity than the bacteria and actinomycetes. Waksman prepared a synthetic medium of glucose, 10 gm.; peptone, 5 gm.;  $\text{KH}_2\text{PO}_4$ , 1 gm.;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ , 0.5 gm.; distilled water, 1000 c.c. This is dissolved by boiling, and enough normal acid ( $\text{H}_2\text{SO}_4$  or  $\text{H}_3\text{PO}_4$ ) is added to bring the reaction to pH 3.6-3.8, requiring from 12 to 15 c.c. of normal acid per liter of medium. To this 25 gm. agar is added, dissolved by boiling, filtered, tubed and sterilized as usual. The final reaction should be pH 4.0. The soil is now diluted in the regular way to only 1/50 to 1/200 of the highest dilution used for the determination of bacteria, and plates are prepared in the regular way. The plates are incubated for 72 hours at 25° C. To obtain an accurate count and a low probable error, 10 plates are prepared. The colonies may be counted after 48 hours, then after 72 hours, due to the fact that in some soils, rich in mucorales, the spreading forms will tend to overgrow the plate in 72 hours. By this modified method, which is also applicable to the enumeration of molds in food preparations, only  $29,400 \pm 1700$  have been found, instead of the impossible figure of  $460,000 \pm 94,000$  per gram by the high dilution plate method for counting bacteria.

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**Blastocystis Species in Culture.**

*Kenneth M. Lynch, Am. J. Trop. Med., 2:215, May, 1922.*

The mediums upon which *Blastocystis* has grown readily include the fluid from an ovarian cyst, several peritoneal transudates of fairly high albuminous content, and liquid human blood serum. Various strengths of these fluids have been used with the result that some of the cells grow best in strong and some in dilute solutions. No cultures have been obtained in a number of attempts to plant the cell on such solid mediums as Loeffler's blood serum, nutrient agar, and Saboraud's sugar agar, or in beef broth, although it is indicated that anaërobic cultures might be successful on solid mediums, since the cell grows in liquid mediums at the bottom of the tube and exposure to air is rapidly destructive. In cultures 3 methods of reproduction were encountered: fission, peripheral gemmation, and endosporulation; although mixed cultures were obtained from many cultures from different individuals, there have emerged 3 distinct types. These types possess certain common features, such as the gross appearance in feces and the processes of fission and budding. There are certain differences between the forms, such as the large size of the budding forms as compared to the fission and sporulating forms, and the optimum strength of the culture media. These may depend on environment or other circumstances not concerned with specific differences.

Lynch believes that in this study on *Blastocystis* from the intestine of man, 3 distinct species have been distinguished by the method of reproduction in culture. The first of these, i. e. that reproducing by binary division and multiple fission, is tentatively identified with *Blastocystis enterocola*, with the reservation that should the processes of multiple division of Alexieff and that of this study be definitely differentiated, the first species of this study will become identified as *Blastocystis hominis*. The second type, reproducing by fission and multiple peripheral gemmation, it is proposed to name *Blastocystis gemmagina*, n. sp., and the third reproducing by fission and endosporulation, *Blastocystis sporogina*, n. sp.

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**A Note on Certain Coprozoic Organisms in Cultures from Man.**

*Kenneth M. Lynch, Am. J. Trop. Med., 2:223, May, 1922.*

From time to time free-living organisms, ingested with food and water, have been confused with intestinal protozoa. These so-called intestinal parasites pass through the intestine of man alive, and do not grow there. In experiments on *Blastocystis*, Lynch encountered several forms of organisms which resembled the fresh water algae and which were easily confused with *Blastocystis*. Lynch states that not many of such organisms grow well at body temperature and when they have been observed it was rather as individuals than as growing cultures.

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**A Source for Material of Protozoan and Other Parasites.**

*Maynard M. Metcalf, J. Parasitol., 8:148, March, 1922.*

Metcalf reports that over 1100 good examples of infections of  
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specimens by opalinids were found in the Anuran collection of the United States National Museum. In many cases the material was sufficiently satisfactory for study of nuclear phenomena which were used in specific distinctions, the number of macrochromosomes being a very usable diagnostic character. Animals that had been from 40-80 years in their hosts in alcohol upon the museum shelves yielded good opalinid material. Other ciliates also were well preserved, as were also trematodes and nematodes. As a preservative agent for anura, alcohol is far superior to formalin. In museums of the above-mentioned type, in working museums, and around most laboratories where there are many jars of unused material, can be found material in which there will probably be parasites well enough preserved for toxonomic study.

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**Cultivable Amebic Parasites of the Human Intestine.**

*A. Gauducheau, Bull. Soc. de path. exot., 15:229, Paris, April 12, 1922.*

Large numbers of Annamite troops were examined in 1916, in consequence of a cholera outbreak. Arrangements were made permitting 1000 stool examinations per hour. The form of ameba previously described by the author under the name *Entamoeba phagocytoides* was clearly found inhabiting the rectum, in diarrheic cases. The ameba is naturally associated with bacteria. The latter vary considerably. *Coli* and *pasteurella* favor the ameba, *staphylococci* are less favorable to amebic growth and *subtilis* and *mesentericus* kill the ameba. The amebas ingest erythrocytes. The pulsating vacuole may be caused to appear or disappear at will. The morphology is affected by differences in the culture media. It was impossible to obtain, by culture, forms resembling those which are not cultivable. The cultivable form derived from the intestine resembles a form occurring in water courses in Indo-China, the latter being easier to cultivate. Uncultivable and intermediate forms sometimes occur in diarrheic stools along with the cultivable type described. There is no transformation of species, but a distinct type capable of inhabiting the human intestine. This type is a facultative parasite, and somewhat resembles the myxameba of the myxomycetes.

The karyosome of the cultivable species is large in proportion to the entire nucleus of true entameba. The cultivable form from the intestine may be properly termed *Endomilax phagocytoides*.

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(1d—40)

(1d—40)

**The Effect of Emetinized Blood and Serum from Man and Cat on Pathogenic *Entamoebae* in Stools.**

*William Allan, Am. J. Trop. Med., 2:195, May, 1922.*

Allan undertook to investigate the possibility of reproducing the toxic effect upon entamebas of emetin hydrochlorid outside the body (1) by mixing emetin with the blood and serum from man and cat, and (2) by injecting man and cat with therapeutic doses of emetin, withdrawing blood after absorption, and then applying these various

mixtures to pathogenic entamebas in stools. A table shows that in the first experiment, in no case did either the human blood and serum or the cat blood and serum mixed with emetin have any effect upon the entamebas. The results obtained from the second experiment show that citrated blood of man and cat, withdrawn after therapeutic doses of emetin have within an hour no effect on entamebas in stools, in dilutions weaker than 1:8. Allan concludes that emetinized human blood is no more toxic for entamebas in stools than emetinized cat blood, within the time limit of one hour.

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(1d—41)

(1d—41)

**Notes on a Microsporidian Parasite of a Nematode.**

*R. Kudo and D. C. Hetherington, J. Parasitol., 8:129, March, 1922.*

Up to the present 5 authors have noted what they regarded as parasites in the intestine and the reproductive organs of *Ascaris mystax*, a nematode of the cat. While examining *Protospirura muris*, a parasitic nematode of the common house mouse, *Mus musculus*, the authors' attention was called to an apparent protozoan parasite in the epithelial cells of the intestine. On examination of the spores it was found that the protozoan was a microsporidian for which the name *Thelohania reniformis* nov. spec. is proposed. The protozoan was found in the epithelial cells of the intestine of the host worm throughout its entire length save the very extremities, and isolated spores as well as those still enclosed in the sporont membrane were also noticed in the lumen of the organ. No other organs of the host nematode showed any degree of infection by the parasite, although the body and particularly the reproductive organs were searched for evidence.

The spore has a comparatively thin membrane and under an immersion objective can be differentiated into 2 regions: near one of the extremities, which is frequently more rounded than the other, there is to be seen a rounded clear area, while the remaining portion is finely granular. The schizont multiplies in number by binary fission; the nuclear division is amitotic. The schizonts become the sporonts which develop into sporoblasts and finally into spores. As far as the writers observed the nucleus of the host cell is not affected by the infection nor does the parasite seem to cause any pathologic changes upon the host organ.

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(1d—42)

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**A New Myxosporidian Parasite of the Channel Catfish, *Ictalurus Punctatus*.**

*H. S. Davis, J. Parasitol., 8:118, March, 1922.*

Of 29 channel catfish examined for parasites 1 was found to be badly infected with a new species of henneguya. This species, named by Davis, *Henneguya plasmodia*, could only be seen under a magnification of about 150 diameters, which showed the small ameboid parasites to be heavily interspersed among the epithelial cells of the gills. All stages from small vegetative trophozoites to adult sporulating forms were abundant. Both vegetative and sporulating types of tropho-

(See. 1—Page 140)



zoites are very irregular in shape with several short, conical pseudopodia by means of which they move slowly about among the epithelial cells. The trophozoites are colorless and distinctly granular with usually no trace of a distinct ectoplasmic layer, although a few were observed in which the ectoplasm was quite noticeable; they probably multiply by plasmotomy or schizogony. Sporulation was the only method of reproduction observed, most trophozoites containing spores in various stages of development. The postcapsular process of the spore, unlike that of other species of the genus, is the same diameter throughout except near the tip where it tapers rapidly to a point. The capsules are large and conspicuous. The sporoplasm, which can be readily distinguished, is finely granular throughout. The *H. plasmodia* spore resembles that of *H. macrura* Gurley and *H. brachyura* Ward but the vegetative stages are very different.

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(1d—43)

(1d—43)

**Review of the Position of the Genus *Haemocystidium* (Castellani and Willey, 1904), with a Description of Two New Species.**

*H. E. Shortt, Indian J. M. Res., 9: 814, Calcutta, April, 1922.*

From a review of the work of various investigators, and after a consideration of all the described species of the genus *haemocystidium*, it is concluded that this genus is synonymous with *haemoproteus*, since in no case are the characters of the parasite sufficiently distinctive to justify the formation of a new genus. It is therefore considered that the genus *haemocystidium*, Castellani and Willey, 1904, should yield to the genus *haemoproteus*, Kruse, 1890, which has priority. The distinction, which was made because all the members placed in Castellani and Willey's genus were found in cold-blooded vertebrates, is artificial and—as Wenyon has pointed out—of no generic significance. The 2 new species presented are the *Haemoproteus phyllodactyli* and the *Haemoproteus grahami*. The former parasite was found in an extremely rare species of gecko, *Phyllodactylus elisae*. It was obtained by the writer at Quritu, on the Persia frontier, in 1920. The young forms are generally situated at the end of the erythrocytes and are often pyriform in shape. The smallest forms seen measure 2.3 by 2 microns. The intermediate forms are somewhat banana-shaped, with bluntly pointed ends, and occupy a position parallel to the long axis of the host-cell. The mature forms must be looked upon as mature gametocytes. Two forms, male and female, are characterized by different reactions to Romanowsky stains. A prolonged search was made of all the internal organs and the bone marrow by means of smears and sections for stages in schizogony, but with the exception of a form in the lung nothing was discovered. In the wall of one of the air spaces of the lung an irregularly oblong body surrounded by a cystlike wall was found. From one side of this wall a second similar but less densely staining body projected outward. Both bodies of the cyst-wall contained numerous and uniformly scattered grains of golden-brown pigment. The lizard which is the host of the *Haemoproteus grahami* is a rock lizard *Agama nupta*, var. *fusca*, common throughout W. and N. W. Persia. In the case of this *haemoproteus*, only forms



present in the peripheral circulation were encountered. A prolonged search of the internal organs revealed no stages in the schizogony of the parasite. The parasites infecting blood cells in the lungs seemed to produce enormous quantities of pigment in abnormally large grains. The small forms were situated at the ends of the host-cells, and the most minute forms measured 3 by 1.5 microns. The intermediate forms generally continued to occupy the end portion of the host-cells, and as they grew in size caused displacement of its nucleus and some deformation of its contour. The mature forms could be differentiated into male and female gametocytes by the differential staining.

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(1d—44)

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**Notes on Two Hemogregarines of Persian Lizards.**

*H. W. Shortt, Indian J. M. Res., 9:287, Calcutta, April, 1922.*

In the hemogregarine of the *Phyllodactylus elisae*, 2 forms of schizogony were met with: (1) Schizogony in the erythrocytes with the production of small cysts and small merozoites; this was found to occur in the erythrocytes contained in the capillaries of the lungs and in the spleen and liver. (2) Schizogony in endothelial cells lining the air spaces of the lungs, with the production of large cysts and larger merozoites. In no other site were these cysts found. In the hemogregarine of *Agama nupta* var. *fusca*, only stages of schizogony comparable to the larger type of cyst in the species already described were met with. No forms of schizogony with the production of the smaller type of cyst were encountered, either in erythrocytes or in endothelial cells. The earliest stages of schizogony appeared to be small oval trophozoites, occasionally seen in small groups or pairs. These apparently had entered endothelial cells lining the air spaces of the lungs and sometimes 2 were encountered in a small cell. They measured 6 by 5 microns. The last stage, or mature cyst, was of large size, measuring 20 by 10 microns, while the containing endothelial cell in a cyst measured 23.8 by 13.2 microns. The chromatin masses were seen to be each associated with a small amount of protoplasm, the chromatin or nucleus of the merozoite occupying one end.

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(1d—45)

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**Herpetomonas Muscae Domesticae, Its Behavior and Effect in Laboratory Animals.**

*R. W. Glaser, J. Parasitol., 8:99, March, 1922.*

While making some observations on the habits of blood-sucking flies, Glaser noted that many of the house flies frequenting cattle were engorged with blood. Closer observation disclosed that house flies frequently feed at the punctures made by *Stomoxys calcitrans* or *Haematobia serrata*. *Herpetomonas muscae domesticae* was found to be the most prevalent flagellate inhabiting the digestive tract of adult house flies in summer. This flagellate parasitized many flies and was sometimes found in such numbers that the entire intestinal tract seemed to contain little else. The greatest degree of parasitism was reached in July and August. The parasitized flies were caught in cow barns and in horse stables. Flies caught in dwellings were not parasitized.

The morphologic characters of this parasite have been described fully by other workers, but Glaser obtained some excellent films from flies fixed and stained by Giemsa's stain which seem to prove that the flagellum is single and that the so-called "double nature" of the flagellum is a division phenomenon. In these specimens the thread which runs backward from the kinetonucleus appeared nearly straight. The author was unable to produce experimental leishmaniasis or herpetomoniasis with *H. muscae domesticae*. These negative results need not reflect on any of the results obtained by Franchini and Mantovani, as these investigators may have dealt with a geographic variety or with a distinct species, although for morphologic reasons the European forms and the form studied in New Jersey may be considered identical. However, in similar experiments on grass-hoppers and locustids, a small number of hoppers inoculated with the intestinal contents of parasitized house flies survived, freed themselves of the intestinal bacteria in 48 hours, and maintained *H. muscae domesticae* for 48 hours or more. On a specially prepared insect horse serum medium the flagellate was obtained in pure culture and reproduced itself by longitudinal division.

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(1d—46)

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**A Note on Some Cultural Phases of *Leishmania Donovan*.**

*Biraj Mohan Das Gupta, Indian J. M. Res., 9: 809, Calcutta, April, 1922.*

A kala-azar patient died. The spleen was removed within twenty minutes. Films showed a very heavy infection with kala-azar, small torpedo-like forms of *Leishmania donovani* predominating. A small portion of this heavily infected spleen was macerated in sterile normal saline and 10 c.c. of the emulsion given intraperitoneally to a monkey whose peripheral blood showed no parasites. For twenty-six days films of the monkey's peripheral blood were negative, and showed no changes. At the end of eighty-five days it was found that the whole blood picture had changed. Films showed numerous normoblasts, megaloblasts, polychromatophile erythrocytes, a diminution in the polynuclear leukocyte count and a marked increase in the number of large hyaline mononuclears. It was further found that the spleen had become palpable. After spleen puncture, films of the spleen juice were negative, and the N. N. N. cultures became contaminated. A liver puncture was made on the eighty-eighth day. Films were negative. On the ninety-first day the monkey was definitely ill, and spleen puncture was again carried out. The films were negative; cultures were positive. The next day adrenalin was given hypodermically and 6 films taken half an hour later from the peripheral blood and most thoroughly searched. No parasites were found. On the ninety-fourth day a third spleen puncture was done. The films showed one very doubtful form. The cultures were positive. On the one hundred and tenth day a fourth spleen puncture was done. Films were again negative and cultures were again positive. By an accident the monkey died. An immediate post-mortem examination showed the spleen 3 or 4 times its usual size and the liver enlarged. Films taken from all the internal organs showed no parasites. On 3 occasions N. N. N. cultures gave a rich yield of *L. donovani* flagellates. The important point in regard to the cultures

is that evidence is steadily accumulating that the *L. donovani* body is capable of encystment. In the midgut of an infected *Cimex rotundatus*, cyst formation occurs. It can also occur in N. N. N. cultures. The history of the infected monkey raises again the question as to whether unrecognized forms of *L. donovani* may not exist in the tissues of its vertebrate host. The aflagellate and granule phases seem to be a phase of the extrahuman cycle or a reaction to unfavorable environment.

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**The Staining of Spirochetes in Cover-Glass Smears by the Silver-Agar Method.**

*A. S. Warthin and A. C. Starry, J. Infect. Dis., 30: 592, June, 1922.*

The dark-field and the India ink methods of demonstrating spirochetes are unsatisfactory and in the hands of inexperienced workers dangerous because of the difficulty of differentiating *Spirochaeta pallida* from organisms of the mouth and smegma. By the method of silver impregnation of spirochetes in smears on cover-glasses here reported the morphologic details of the organisms are so accentuated that diagnosis is easy. The technical directions are as follows: Prepare smears on No 1 cover-glass, dry thoroughly in air, place in absolute alcohol three to five minutes, wash in distilled water. (To clear the background, the smear may be placed in concentrated hydrogen peroxid for five to twenty minutes and then washed thoroughly in distilled water.) Rinse cover-glass with smear in 2% silver nitrate. Cover the smear side with another clean cover-glass rinsed in the silver nitrate solution. Place the adherent pair of cover-glasses carefully, so as not to separate them, in a bottle containing 2% silver nitrate solution, and put in an incubator for one to two hours; then remove the cover-glasses from the solution and separate them. Place the cover-glass (smear side up) in a mixture of 2% silver nitrate solution (3 c.c.), warm 10% aqueous gelatin solution (5 c.c.), warm glycerol (5 c.c.), warm 1.5% agar suspension (5 c.c.), 5% aqueous hydroquinone solution (2 c.c.). After the solution is reduced remove and rinse in 5% sodium thiosulphate solution. Rinse in distilled water. Pass through absolute alcohol, xylol, and balsam.

Except for the time necessary for silver impregnation in the incubator the method is relatively short. Although its greatest value is in the clinical diagnosis of syphilis, it is useful also in the recovery of spirochetes from the organs of inoculated animals or from blood or urine and in the study of other strains of spirochetal organisms.

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(1d—48)

(1d—48)

***Pseudoleptospira Icterohaemorrhagiae*.**

*Ralph W. Mendelson, J. Trop. Med. & Hyg., 25: 125, London, May 15, 1922.*

Out of 1483 rats examined by Mendelson in Siam, 8 were found to harbor an organism which morphologically closely resembled *Leptospira icterohaemorrhagiae* Noguchi. All attempts at cultivation failed.

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To secure absolute anaërobic conditions the Mendelson modification of a Noguchi anaërobic apparatus was used. The organism isolated from the kidney varied in length from 5-30 microns, with 1-6 waves, either large or small. Inoculations of the organism into a monkey and 7 guinea-pigs were all negative. Due to this negative pathogenesis and the fact that Mendelson has never seen a case of infectious jaundice in Siam, he considers the organism as an innocent parasite, and until further reported on suggests the name, *Pseudoleptospira icterohaemorrhagiae*.

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**The Relapsing Fever Spirochete of Panama.**

*J. Harold St. John and Lewis B. Bates, Am. J. Trop. Med., 2: 251, May, 1922.*

The Panama strain of the relapsing fever spirochete, which has recently been described, has now been conclusively proved to be a distinct species of the relapsing fever spirochete, if these spirochetes may be divided into species. The writers made comparative studies of *Spirochaeta obermeieri*, *S. novyi*, *S. kochi*, *S. duttoni* and the Spirochete of Panama, by inoculating white rats, and white mice which had recovered from each of these infections with the Spirochete of Panama; by inoculating white mice which had been hyperimmunized against each of these infections with Spirochete of Panama; and by ascertaining the effect of immune serum of each of these spirochetes upon each spirochete, both by dark-field examination and by animal inoculation. The results of the agglutination experiments show that a very close relationship exists between the 4 spirochetes of Obermeier, Novy, Koch and Dutton. A hyperimmune serum does not suffice to distinguish these strains. Strong immune serums from the 4 other spirochetes had no effect on the Spirochete of Panama, showing that serologically this strain is unrelated to the other 4. Spirochete of Panama was not injured by incubating with any of the 4 other spirochetes or normal serums, but was killed by incubating with Panama serum. A series of protection experiments also showed the Panama relapsing fever spirochete to be a single species. The writers believe that relapsing fever in Panama is, in all probability, due to one species, variety or strain of the relapsing fever spirochete, namely Spirochete of Panama.

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**A Study of *Trypanosoma Americanum*.**

*R. W. Glaser, J. Parasitol., 8: 136, March, 1922.*

On using cattle blood for other work, Glaser encountered the very large hemoflagellate first described by Crawley under the name of *Trypanosoma americanum*. This parasite was then experimentally successfully grown in horse blood medium and in the N. N. N. medium, as well as in cow blood medium. The morphologic, cytologic and cultural characters noted are those already fully described by Crawley. In freshly drawn blood and in very early cultures *T. americanum* resembles the majority of the forms found in 3 and 4 day old cultures.

Inoculations of laboratory animals, guinea-pigs, rabbits, rats and  
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wild mice with 3-4 day old cultures gave negative results, thereby demonstrating the specificity of *T. americanum* for cattle. To determine whether some insect might act as the transmitter of this parasite, the insect fauna occurring around the cattle that harbored trypanosomes was carefully studied and only 3 forms appeared worthy of consideration, i. e. *Stomoxys calcitrans*, *Haematobia serrata*, and *Musca domestica*. These flies were carefully dissected and the entire alimentary canal, including the crop, salivary glands and malpighian tubes, was examined, but no trypanosomes were found. Experiments performed to determine whether *T. americanum* could survive in these flies showed that stomoxys and haematobia might act as transmitters of *T. americanum*, for the flagellate survived for 48 hours within them, but the transfer from host to host must be made within that time.

Morphologic and experimental data show that *T. americanum* is structurally a crithidium. Prolonged culture and environmental alterations have a tendency to produce herpetomonad types but never trypanosome types. Although morphologically this parasite resembles a crithidium, but lives in the blood of cattle, Glaser thinks it best to regard it as an intermediate evolutionary stage between the true crithidians and true trypanosomes, and retain the name *T. americanum*.

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#### **Measurement as the Basis of Diagnosis of the Furcocercous Cercariae.**

*Frank Milton, Indian M. Gaz., 57: 161, Calcutta, May, 1922.*

Milton has collected measurements in 22 species of furcocercous cercariae, taken in Egypt, India, the Cape and both North and South America; the series is thus representative of the parasites found in widely separated parts of the world. In spite of the different conditions and methods under which these measurements have been recorded, they are all capable of being brought into certain well-defined classes, and the grouping thus arrived at appears to be supported by a similar grouping of the molluscan hosts in which the individual cercariae develop.

In Group 1 are found cercariae in which the rami of the tail are markedly shorter than the stem, the difference being as 1:2 or even greater, and in which the body, while it is longer than the rami, is shorter than the stem. In Group 2 are cercariae in which the rami and stem are nearly equal, the stem being slightly longer than the rami, and either of these longer than the body. In Group 3 are cercariae in which the rami and stem are of equal length and in which either of these is less than the length of the body. These groups are again divided into subgroups. Group 1, Subgroup A, i. e. apharyngeal and non-eye-spotted cercariae, contains all the at present known schistosomes parasitic in man, together with *Cercaria spindalis*, a schistosome of bovines, and the uncertain forms *C. indicae* XXX and *C. spinosa*. Group 1, Subgroup B, contains only apharyngeal eye-spotted forms and probably represents the true schistosomes parasitic in birds. Groups 2 and 3, consisting of forms with a more or less well-developed pharynx are not schistosomes and as the subsequent development of



none of them has yet been made out, it is impossible to identify them.

Should further research uphold Milton's classification, we shall have arrived at a clear definition of a schistosome cercaria as being a furcocercous distome cercaria characterized by the absence of a pharynx and possession of a tail, the rami of which are less than half the length of the stem, and with a body intermediate in length between that of the stem of the tail and its rami.

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(1d—52)

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**The Rat Tapeworm, *Hymenolepis Diminuta*, in Man.**

*William A. Riley and W. R. Shannon, J. Parasitol., 8: 109, March, 1922.*

Cases of the occurrence of the rat tapeworm *Hymenolepis diminuta* as a parasite of man are of such rarity as to merit special record. An unreported case of rat tapeworm in a female infant, 9 months of age, is described in detail. The mother, who brought the child to the Miller Hospital Clinic, stated that the baby was suffering from an intestinal upset, with green, foul-smelling stools in which worm segments had been observed. Examination of the stools showed numerous segments. The child was also treated for an eczema. Following this first visit the baby apparently improved so that the mother did not return, in spite of the fact that she had been advised of the necessity of placing the baby in the hospital for treatment for the tapeworm. She returned 3½ months later reporting that the child was restless and was remaining stationary in weight. Treatment was given to the child, but it was only partially satisfactory, for although about 20 worms were recovered, careful examination failed to reveal any complete specimens, and at the time this article was written, segments were still present in the stool. The discharged worms agreed in every respect, with the exception of the scolex characters which were not available, with descriptions and specimens of *H. diminuta*. The infection was probably obtained when the baby was allowed to creep on a grassy plot.

The sources of infestation, which have been reported by other workers, are rats, mice, the body cavity of a surprising range of meal-infesting insects, beetles, myriapods and rat fleas. A total of 61 infections are known for man. Out of 54 cases, 14 were found in children ranging in age from 9 months to 12 years; 3 were noted merely as children; 15 were adults, 10 of them having been brought to light through the examination of troops; concerning 22 the writers have no available data. In this connection it is of interest to note that, so far as published, extensive examination of troops in this country have not revealed cases of *H. diminuta* infestation.

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**A New Rat Tapeworm, *Schizotaenia Sigmodontis*, from North America.**

*Asa C. Chandler and Charles L. Suttles, J. Parasitol., 8: 123, March, 1922.*

While the authors were engaged in an examination of rats of  
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various kinds for evidence of plague infection, a considerable number of specimens of the East Texas cotton rat, *Sigmodon hispidus texianus*, were brought to the laboratory for examination and were found to harbor a tapeworm of the family Anoplocephalidae which proved to be a new species. In general anatomy and morphology, except with respect to the uterus, it resembles *Schizotaenia americana*, though in the branched excretory system and relative enormous cirrus and cirrus pouch it approaches *S. anoplocephaloides*. The authors give the new species the name of *Schizotaenia sigmodontis*, n. sp., Chandler and Suttles, 1922, with the following diagnosis: Strobila 21.5-65 mm. long by 2.5-3.5 mm. in maximum breadth, segments, except sometimes terminal ones, broader than long. Proglottids 70-90. Scolex unarmed, about 0.38 to 0.45 mm. in diameter, about half this length, not sharply demarcated from the neck; suckers 0.16 mm. in diameter. Strobilization begins about 0.6 mm. from anterior end. Genital pores regularly alternate, near middle of lateral margins of segments. Cirrus very long, spinous; cirrus pouch large, containing enlargement of seminal vesicle which, medial of cirrus pouch, is slightly convoluted. Testes about 70 in number, 60-85 microns in diameter, in posterior band in median field, more numerous on aporose side, female genital glands slightly displaced toward pore side; ovary crescentic; yolk gland bilobed with radiating lobules; shell gland large; uterus develops as radiating out-pocketings from ovary itself, eventually occupying entire median field as coarse anastomosing branched pouches; ova globular, with 3 membranes and pyriform apparatus; outer shell 47-53 microns in diameter, oncosphere 16-18 microns in diameter, pyriform apparatus 10 microns long. Calcareous corpuscles present.

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**Notes on Some Indian Aphiochaetae. Aphiochaeta Xanthina Speiser (Repicta Schmitz; Circumsetosa de Meijere; Ferruginea Brunetti), Whose Larvas Cause Cutaneous and Intestinal Myiasis in Man and Animals, and Aphiochaeta Rufipes Meigen, Whose Larvas Occasionally Cause Cutaneous Myiasis in Animals.**

*W. S. Patton, Indian J. M. Res. 9: 683, Calcutta, April, 1922.*

The eggs of *Aphiochaeta xanthina* Speiser measured 0.02 inch in length, are boat-shaped, and of a silvery white color. A narrow scalloped frill extends around the egg rather nearer the lower than the upper surface. The upper surface is covered with about 16 rows of about 60 snow white, short, recumbent spines. The ventral surface is ornamented with regular hexagonal markings. The eggs hatch in from twenty-eight to thirty-six hours. The mature larva is  $\frac{1}{6}$  in. long, and is of a dirty white color. The whole cycle from the egg to the adult occupies from twenty-one to twenty-seven days. The adult head is broad and yellowish brown; the eyes are black, widely separated and covered with minute hairs. The thorax is yellowish brown; the abdomen in the female is yellowish brown, sometimes quite light but usually dark brown, in the male the dark markings are nearly always much more extensive, often only leaving white dots or stripes on the dorsal surface. On the external genitals of the male the 2 stiff bristles at the

apex of the finger-like process, which appear to be the homologue of the superior clasper, are very characteristic of this species. The legs are pale yellow with numerous hairs and bristles, the wings whitish yellow with 2 short rows of stout bristles along the upper border of costa, extending to the bifurcation of the third vein. Of *Aphiochaeta rufipes*, the mature larva is  $\frac{1}{6}$  in. long and of a yellowish white color, similar to the larva of *A. xanthina*. The prothorax of the larva of *A. rufipes* is, however, armed with a small semilunar plate of chitin on its dorsal surface, the convex side of the plate being directed towards the head. The anterior spiracles project from the sides of the segment, their apices formed of small chitinous knobs. The adult head is somewhat narrower than that of *A. xanthina*; the eyes are black, widely separated, and only sparsely covered with hairs. The thorax is dark brown, often with a reddish tinge, and in dried specimens appears almost black, covered with minute hairs. The abdomen is dark brown, the ventral surface light yellow. The wings have a double row of short bristles on the costa, extending up to the bifurcation of the third vein.

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**Some Notes on Indian Calliphorinae. Part VI. How to Recognize the Indian Myiasis-Producing Flies and Their Larvas, together with Some Notes on How to Breed Them and Study Their Habits.**

*W. S. Patton, Indian J. M. Res., 9: 635, Calcutta, April, 1922.*

The Calliphorinae or blow-flies are large green or blue insects, often with a characteristic brassy sheen. The myiasis-producing species belong to 2 genera, *Lucilia* and *Chrysomyia*. In *Lucilia* the bristles on the thorax are well developed, forming 2 distinct rows down the middle of the thorax in front and behind the suture. The thorax, and in most species the abdomen, is unbanded. In *Chrysomyia*, on the other hand, there are very few bristles on the thorax, and then only one row on each side, but instead the thorax is covered with downy hairs. The thorax has indistinct longitudinal bands, and the abdomen well marked horizontal bands at the bases of the segments. In determining the genus to which a larva belongs, if the posterior spiracles are comparatively large and enclosed, either in a shallow cleft or a deep hollow formed by the end of the eighth abdominal segment, the larva is either that of a species of *Chrysomyia* or *Sarcophaga*. If the end is compressed from before backwards so as to draw the lips of the slit back, in a larva of *Chrysomyia* the posterior spiracles at once become visible; they can be seen as 2 large somewhat D-shaped plates, with 3 brown slits directed downwards and inwards. • The segmented spines are well developed, and as a rule the anterior spiracles have only a few processes. If, on the other hand, on examining the end of the larva it is noted that the posterior spiracles are exposed without compressing the end of the larva, and are not (or only partially) hidden in a cleft, and in addition are round or slightly pear-shaped, and comparatively small, the larva belongs to a species of *Lucilia*. The commonest larva found in cases of myiasis in man and animals is *Chrysomyia bezziana*. It is important to distinguish its larva from that of the

common bazaar species *Chrysomya megacephala*. The larva of *C. bezziana* is of a creamy yellow color, while that of *C. megacephala* is whiter and softer. The two ends of the larva of *C. bezziana* are usually much darker than those of the larva of *C. megacephala*, and the felts of spines are much better developed. The spines of the larva of *C. megacephala* are not so prominent. The larvae of *C. bezziana* cannot be reared to maturity in meat or the dead body of an animal. They will live only in living tissues, and can be easily reared in the wound on the body of an animal. The larvae of *C. megacephala*, *Lucilia argyricephala*, *Sarcophaga* and *Aphiochaeta* can, on the other hand, be easily reared to maturity in decaying meat.

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#### **Observations on the Poisonous Nature of the White Marked Tussock-Moth.**

*Harry H. Knight, J. Parasitol., 8: 133, March, 1922.*

A report is made of definite proof of the poisonous nature of the white-marked tussock-moth, which is believed by many entomologists to be nonpoisonous. A man, while collecting these moths from trees on the Minnesota University campus, had to discontinue work because of numerous swellings on his face, neck, and arms. These later became painful and some fever resulted. The physician was unable to diagnose the trouble as hives. At the same time while handling the cocoons, Knight experienced itching and burning sensations on the forearm and began to suspect that the tussock-moth cocoons were the source of the trouble. Seven people were tested for the toxic effect from the cocoons and larvae, and in each case swelling and painful results followed. It was found that the poisonous hairs of the tussock-moth caterpillar are located in the prominent tufts on the dorsal surface. When these tufts were rubbed against the skin, groups of barbed hairs could be seen under the lens, apparently hooked in the skin. These hairs would easily break, and could scarcely be removed by aid of forceps.

The accepted opinion that caterpillars of this variety are nonpoisonous may be due to the fact that the poison is apparently developed only in the late instars of larval life. Knight tested the toxic effects of one half-grown larva and found that it failed to react. The mucilaginous pulp of purslane leaves applied to the swellings gave pronounced relief.

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### **1e. IMMUNOLOGY; SEROLOGY AND HEMATOLOGY.**

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#### **Immunity in Relation to Transplanted Tissue.**

*Moyer S. Fleisher, J. Med. Research, 43: 145, April-May, 1922.*

Fleisher reports the results of his studies on the reactions occurring in the neighborhood of tissue transplants in animals immunized to animals of other species—heterotransplants—and particularly the fate of the heterotransplant in the immunized animals as compared to non-immunized. Mouse kidney was transplanted into normal rats and into

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rats which had previously been immunized by intraperitoneal injections, at intervals of two days, of mouse kidney, freshly removed and ground, the implantations of kidney being made twelve to fourteen days after the last immunizing injection.

As compared with the normal animals, the leukocytic reaction about the heterotransplant in the immunized animals was very marked, consisting of both mononuclears and polynuclears, but lasted for only three or four days after transplantation. This more marked leukocytic reaction was noted both about the periphery and in the peripheral portions of the tissue, but whether the two manifestations are parts of one and the same phenomenon and due to the same cause, or whether they are distinct and due to different causes has not been determined. There appeared to be also in the immunized animals a slightly slower invasion of the transplanted tissue by the leukocytes or else a somewhat slower clearing of the periphery of the transplant as a result of the greater leukocytic reaction. In general, the connective tissue reaction about the tissue was the same in the normal and in the immune animals, but in the latter there appeared to be a slower invasion by the connective tissue, and in the later stages the transplanted tissue appeared to be more compact and better preserved. Practically no other differences between the tissue transplants in normal and in immunized animals were noted.

Transplantation into immune animals appeared to have little or no effect on the kidney epithelium. In the first two days the regeneration and preservation of the epithelium and tubules were slightly less in the immune animals, corresponding with the period of greater leukocytic reaction in these animals, but later no differences could be observed. These differences between transplants in normal and in immunized animals are present whether the transplants are made subcutaneously or intraperitoneally, but in general the leukocytic reaction was less marked and the epithelium less well preserved in intraperitoneal transplantations.

The conclusion is that in animals immunized to the tissues of a different species some of the reactions of the host tissues are modified, but that the immune reaction has no marked effect on the epithelium of the transplant, from which it may be inferred that immunization has not caused the host body to develop substances which are capable of destroying the tissue against which the animal has been immunized.

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### **The Bacteriophagic Virus of D'Herelle.**

*César E. Pico, Semana méd., 29:265, Buenos Aires, April 27, 1922.*

D'Herelle bases his belief in the existence of a filtrable virus upon the following hypotheses: (1) The bacteriolysis obtained by filtration of broth cultures of fecal material is transmitted in series by new cultures of the bacteriolysins, without diminishing the activity of the lytic principle, i. e., the virus is renewed indefinitely at the expense of the bacteria which produce it. (2) Zones of lysis produced upon the surface of agar cultures of bacteriolysins led to the assumption of

a bacteriophagic action. (3) On the basis of the effect of antiseptics (especially fluorids) upon ferments d'Herelle has assumed the bacteriophagic principle to be an active organism sensitive to fluorids, chloroform, quinin, and other antiseptics. (4) The finding of antilytic serum led to the belief in the uniformity of the bacteriophagic principle of the different species of bacteria, excluding the action of specific ferments associated with the various organisms.

Pico considers these arguments inconclusive, and cites alternative theories. According to Kabeshima, the resistance of bacteriophages to heating at 60°-70° C. excludes the existence of a filtrable virus. He considers the lytic principle to be a catalyzer activating a prodiastase contained in the microorganisms, which can be regenerated. According to Cordet and Ciuca, transmissible lysis has been produced, causing "hereditary nutritive vitiation" of *Bacillus coli*, due to leukocytic ferments. The lysis is produced at the expense of the organisms. Bail and others consider bacteriophagia a factor in the bacterial mutations and variations which act, within the organism, as a defensive force against infection. They believe that the lytic principle is produced by the same organisms. Kuttner obtained a lytic principle by extracting the enzymes of the hepatic and intestinal tissue, with glycerin, and filtering. Bachman and Aquino produced transmissible lysis by means of solutions of pancreatin and venom from *Lachesis alternatus*. Pico's own experiments concerned the action of intestinal substances and ferments upon dysentery bacilli; he endeavored to demonstrate the lytic effect of pancreatin and trypsin upon nonautolyzable bacterial strains, in releasing the transmissibility of the phenomenon.

Transmissible lysis was obtained by means of papain and papayotin, warmed to 100° C. A lytic principle was obtained in vitro with ferments extracted from leukocytes by means of HCl, slightly alkalized with NaOH. In view of the destructive action of acids on bacteriophagia, contamination of the leukocytes cannot be assumed. Pico also produced lytic areas and the modifications characteristic of resistant colonies. The importance of these experiments lies in the fact that they produced the phenomena of d'Herelle without their being attributable to a filtrable virus. This renders d'Herelle's theory untenable. Pico attributes bacteriophagia to an acceleration of normal bacterial autolysis. The regeneration of the lytic principle at the expense of the disintegration products of the organisms explains the seriation of the autolysis. A new method of "lysinotherapy" may be based upon these findings.

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**Bacteriophage Phenomena with *Staphylococcus Aureus*.**

*Bessie R. Callow, J. Infect. Dis., 30: 643, June, 1922.*

The presence of a bacteriophage principle transmissible in series against *Staphylococcus aureus* was demonstrated in the pus in 16 staphylococcus infections (boils, carbuncles, cellulitis, etc.). In 2 of these the lytic principle was active against the autogenous strain as well as against other staphylococcus strains; in 6 others it was lytic for one or more heterologous strains, but not for the autogenous strain, in spite of repeated tests. A staphylococcus bacteriophage isolated from vaccinia



and carried through several generations was specific for all the strains with which it came in contact. It was difficult to increase the action of the bacteriophage isolated from the boils beyond the second or third generation; in successive generations it either remained constant or diminished in strength. The vaccinia bacteriophage, on the other hand, showed a marked increase through the fourth generation, at least, and did not deteriorate.

The experiments were too few to justify conclusions as to the period of infection at which a bacteriophage appears, or the length of time for which it persists. In one case lytic material was present in both blood and pus at one time and in neither a few days later, indicating that the bacteriophage may be present in an infected lesion for a limited period, perhaps only until all susceptible organisms have been destroyed.

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**The Immunizing Influence of Protozoa in Infectious Diseases.**

*Michal Poray Gedroyé, Polska gaz. lek., 1:376, Cracow, May 7, 1922.*

Some protozoa have shown themselves to be bacteriophagic. The number and variety of bacteria necessary for the nourishment of the protozoa may be changed at will. The proteins and toxins of the bacteria have no influence on the protozoa. The author attempted to see whether the protective substances of the protozoa could be used in therapy. He chose *Paramecium aurelium* and the fixed virus of hydrophobia. Experiments made on 30 rabbits showed a submeningeal injection of heated paramecium + fixed virus was sufficient to immunize the animal against subsequent injections of a mixture of fresh paramecium culture and fixed virus. Animals which were not previously inoculated died regularly as a result of the second injection. There was copious development of bacteria (bacilli and cocci) which were uncommonly toxic if the culture of paramecium and fixed virus were kept at a temperature of 31°-37° C. for a long time. The rabbits died within eight to twenty-four hours after subdural injection of this substance. The bacterial toxins were always innocuous if an emulsion of fresh paramecium was added immediately before the injection.

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**Hydrogen-Ion Studies. V. Changes in the Reaction of the Blood in Experimental Infections.**

*Edwin F. Hirsch and J. Lisle Williams, J. Infect. Dis. 30:664, June, 1922.*

Since it has been shown that the entire range of reaction of the blood compatible with life lies between pH 7 and pH 7.8, minute changes are seen to be significant. It has been shown also that in rabbits the alkaline reserve of the blood is lowered in experimental infections. There are but few reports, however, of the determination of the reaction of human blood in acute infections. In the present study the reaction of the blood of rabbits infected experimentally with



*B. typhosus*, *B. dysenteriae*, *B. paratyphosus*, *B. enteritidis*, or *B. mucosus*, was determined according to the gas-chain method. It was found that in rabbits the intravenous injection of a suspension of pathogenic bacteria was followed by a diminution of the alkalinity of the blood as well as by a decrease in its alkaline reserve. In those rabbits in which the changes were marked, death occurred; those showing only moderate changes recovered. It was concluded also that the hydrogen-ion concentration of the blood may become so great that the reaction changes to slightly acid.

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**Immunization or Response of Immunized Animals to a Small Dose of Antigen Administered at a Long Interval After First Immunization.**

*W. F. Harvey, Indian J. M. Res., 9:740, Calcutta, April, 1922.*

The agglutination effect of intravenous inoculation of typhoid antigen in pigeons shows a diminution month by month after the inoculation. The drop is marked between the tenth and twentieth day, and very slow thereafter. The condition, based on a twelve months' trial, seemed to reach a constant low level, which was, however, higher than that of the uninoculated animal. The introduction intravenously of a dose of antigen  $\frac{1}{10}$  to  $\frac{1}{20}$  smaller than the original dose, and even smaller still, called for an agglutination response in the pigeons inoculated 12 months previously, which was significantly greater than that elicited in uninoculated pigeons receiving the same doses.

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**Nonspecific Modification of the Formation of Immune Bodies.**

*H. Hajos and F. Sternberg, Ztschr. f. Immunitätsf. u. exper. Ther., 34:218, Jena, May 11, 1922.*

Rabbits were injected simultaneously or in succession with paratyphoid-B bacilli and sheep erythrocytes. The formation of the two agglutinins proceeds independently. Even the normal antibodies (hemagglutinins) undergo no change during the immunization with any kind of antigen. Sodium chlorid, calcium chlorid, potassium chlorate (2 c.c. of each injected in 10% solution), antipyrin, sodium salicylate, morphin, strophanthin, atropin, pilocarpin and adrenalin, when injected into rabbits before, during and after immunization produce absolutely no effect on the agglutinin curve. Slight changes do not vary from the normal daily fluctuations. Injections of adrenalin cause no immediate or subsequent effect on the formation of agglutinins in typhoid patients and convalescents. Only injections of milk cause increased formation of agglutinins in rabbits, lasting for several days.

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**On the Immunizing Properties of Allied Organisms and Non-specific Organisms.**

*W. F. Harvey and K. R. K. Iyengar, Indian J. M. Res., 9:376, Calcutta, April, 1922.*

In this set of experiments with pigeons and with *Bacillus avisep-*  
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ticus, the method adopted was to give the prophylactic doses—in this case the equivalents of 0.5 to 1 mg. dried antigen—intravenously, following the second of these inoculations 12 days later with a dose of the living test organism. A control series of animals was inoculated with the living specific organism to show the mortality for the uninoculated. The prophylactic use of a specific organism demonstrated a great saving of life (15 animals out of 15), as compared with a control series in which there was great mortality. The prophylactic inoculation of an allied organism, *B. cuniculisepticus*, showed no evidence of any greater saving of life than did the prophylactic inoculation of a wholly nonspecific organism. Distinct evidence of protection by the prophylactic inoculation of a nonspecific organism was demonstrated.

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**Double Immunization with Euglobulin and Albumin from the Same Blood Serum.**

*R. Doerr and W. Berger, Klin. Wchnschr., 1:949, Berlin, May 6, 1922.*

Dale and Hartley have demonstrated the plurality of the antigens of the blood serum and the presence of at least 3 main parts of the serum protein (euglobulin, pseudoglobulin, albumin) which may act as antigens. They are distinguished by the specificity and time reactions of their effects. The authors have verified these statements and also found that there are certain differences in specificity and biologic activities in the various subdivisions of the albumin fraction. Serum albumin is an antigen of reduced effect. Successive reduction of the degree of effect of the protein fractions in the salting out series (euglobulin, pseudoglobulin and albumin) goes with changes in the specificity. This shows that the protein fractions of a blood serum have differences in chemical structure which determine their specificity. A serum injection is a competitive immunization with several antigens. Sensitization of a guinea-pig with a number of equal portions of euglobulin and albumin results in a reaction on the part of the animal to each of these antigens, just like that in animals injected with only one protein. The use of a mixture in which the albumin predominates results in no influence on the optimal globulin dose, whereas a surplus of globulin completely suppresses the antigenic function of an otherwise optimal quantity of albumin. The profound difference between albumin and euglobulin is more exactly shown than by mere difference in specificity. There is a more effective and also a less effective antigen and it is possible better to understand the nature of the immunization stimulus by a demonstration of the one-sided prevalence in a cross competitive test of the problems of anaphylaxis and serum disease.

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**Hyperproteinemia after Protein Injection. An Experimental Contribution to the Pathology of Serum Protein and Protein Therapy.**

*Wilhelm Berger, Klin. Wchnschr., 1:1053, Berlin, May 20, 1922.*

After parenteral administration of protein there is an increase  
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in the protein content of the serum of the treated animal, consisting of an increase in globulin and a decrease in albumin. In rabbits treated parenterally with horse serum and suspension of erythrocytes it was found that between the fourth and thirtieth days there was an increase of globulin and between the thirtieth and sixtieth days a second period of absolute and relative increase of albumin; the hyperproteinemia was fully developed 100 to 120 days after the last injection. In the first week after the last injection the fibrin globulin is also increased, indicating a certain sequence (fibrin globulin, serum globulin and serum albumin increase) in the same order as decreasing immunity reaction. The multiplicity of phases and the cellular character of most reactions induced in the blood by the same causes, indicate a cellular regulation of the protein variations. The emaciation, the negative nitrogen balance, the sequence, and the behavior of the erythrocytes suggest the probability of increased surrender of protein by certain cell complexes. Whether the cell complexes give up mostly fibrin globulin, serum globulin or serum albumin depends on their functional condition. The hyperproteinemia in immunization seems to be related to breaking down of tissue, and similar variations in protein are observed in infectious diseases, hunger and other pathologic reactions. There are close relations between immunization and increase in albumin, but the increased discharge of protein into the blood and the amount of precipitin are not directly interdependent. Clinically the long duration of the protein variation is important and also the fact that protein increase is not always found in increased blood density. Hence isolated refractometric determinations do not give a reliable measure of the water balance.

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**Influence of the Heterogenous Proteins on Phagocytosis,  
Studied in the Organism.**

*Ada Dominici, Pediatría, 30:446, Naples, May 15, 1922.*

Experimenting with the injection of bacteria and proteins in the peritoneal cavity of the guinea-pig it was noted that whatever the quality of the protein inoculated, whether very complex (milk) or in course of disintegration (peptone) or used in an already marked degree of lysis (decomposed vaccine, stomosina), and however diverse the protein intoxication derived from them, the reaction of the organism tends in every case to equalize the effects of it, to the point of real defense, by means of 2 phenomena; the rapid progressive reduction and then the disappearance of the bacteria liberated in the peritoneal exudate, on the one hand; on the other the production of an active phagocytosis. This suggests that the various proteins, to act in this uniform manner, must undergo a rapid denaturization, probably under the influence of ferments contained in the peritoneal lymph, or in part coming from the leukocytes, giving rise to products that have a chemotropic action more or less marked.

The phenomenon that dominates the scene by its constancy, and upon which seems to depend the progress and the issue of the infective process, is the phagocytosis: the phagocytic value is weak and slow in the guinea-pig that is destined to succumb, but is quite

lively on the other hand in the animal that will survive the infection. The fact encountered, that the higher phagocytic values follow soon after the inoculation of the infecting material, excludes the idea that the phagocytosis may represent a secondary phenomenon, consequent upon the eventual action of other germicidal influences.

Large doses of proteins act by paralyzing the phagocytic activity, at the same time increasing the morbid process and rendering it mortal. Weak doses, on the contrary, stimulate phagocytosis and perhaps determine the beginning of a light leukocytosis by which is made possible also a partial extraleucytic bacteriolysis, bringing about the rapid resolution of the disease.

In the face of the great mass of facts shown in favor of generic proteinotherapy, some reservation must be made for particular cases as to eventual specific reactions which may arise from some protein materials (perhaps only those already decomposed), whose original character was of a specific nature.

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**The Mechanism of Infection and Vaccination in Cholera through the Oral Tissues.**

*S. Masaki, Ann. de l'Inst. Pasteur, 36: 399, Paris, May, 1922.*

The author's studies were made on guinea-pigs and rabbits. Cholera vibrios, injected into the veins, peritoneum, or under the skin, may be largely recovered from the intestine. Animals swallowing the vibrios are not infected. Bile, sterilized for an hour at 100°, was fed night and morning, the test-animals' stomachs being kept empty. So treated, the animals became sensitized, and the intestinal wall was modified. Normally, the vibrionic proteins (endotoxins) do not pass through the intestinal wall. In animals treated by mouth with bile, passage through the intestinal wall of the bacterial products was shown by the production of agglutinin occurring on feeding killed or living vibrios to the animals. Preventive antibodies are not formed by feeding killed or living vibrios, whether the test animal is sensitized by the bile or not. Rabbits so sensitized are killed in 1-2 weeks if fed with large quantities of virus (2 Roux dishes containing cultures). Moderate doses (1 culture dish) cause sickness for several days. Small doses (half a dish) produce no disturbance. Animals sensitized by feeding with bile and made sick by subsequent feeding with living vibrios become vaccinated against a surely fatal intravenous dose of the living vibrios. The immunity thus acquired is probably local and intestinal.

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**Immunologic Studies on Types of Diphtheria Bacilli.**

*William H. Park, Anna W. Williams and Alice G. Mann, J. Immunol., 7: 243, May, 1922.*

Two series of observations which have been made concerning the degree of protection afforded by a monovalent diphtheria antitoxin seem to give sufficient evidence that the toxins produced by the dif-

ferent strains of the diphtheria bacillus are alike at least in their affinity for antitoxin. The first is, that for the past 25 years, ever since diphtheria antitoxin has been used in practice, injections of a monovalent antitoxin in hundreds of thousands of persons known to be in contact with infection, have given practically complete protection for 2 weeks, i. e. the period during which antitoxin is known to remain in appreciable amounts in a human being after injection.

The second series of observations on routine virulence tests throughout the world, have shown, with a few exceptions, that a monovalent diphtheria antitoxin is able to protect animals given a dose of culture fatal to others not given antitoxin. The authors' experimental work has shown that while the group of diphtheria bacilli contains strains belonging to several agglutinating types, the toxins formed by these different types are qualitatively alike and, from the practical standpoint, quantitatively so. Strong toxin from any diphtheria bacillus strain is suitable for the Schick test and for immunization of man or animal. A monovalent antitoxic serum is suitable for protective and curative measures against all diphtheria strains.

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**Report of the Committee on Standard Preparation of Diphtheria Antitoxin.**

*Am. J. Pub. Health*, 12: 503, June, 1922.

The paucity of new work in antitoxin preparation has quite generally been due to the poor success frequently experienced in the preparation of diphtheria toxin. Although some progress has been made in the quest for a suitable substitute for Witte's peptone, no substitute on the market gives uniformly satisfactory results. Some manufacturers prefer to make their own peptone. With these peptones of not very uniform composition the reaction of the broth must be adjusted very carefully to pH 7.4-7.6. The period of incubation of the toxin is more variable with American peptones than when Witte's peptone was used; it may vary from three to nine days. The committee, however, is of opinion that on the whole the knowledge of the conditions affecting toxin production has advanced sufficiently to demonstrate that efficient diphtheria toxins can be prepared by the use of American peptones. In the refining of the product very little progress has apparently been made. Some difficulty has been experienced in obtaining a suitable quality of tricresol which is generally used as a preservative. The time for the adoption of uniform methods has not yet arrived.

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**Do Mast Cells Appear during Antirabic Treatment?**

*A. Rochaix, J. de physiol. et de path. gén.*, 20: 77, No. 1, Paris, 1922.

Antirabic vaccination produces progressive leukocystosis. Rochaix has examined 3 human cases under the antirabic treatment, 2 rabbits inoculated with infected spinal cords and 2 others inoculated with

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normal nervous tissue. Basophilic polynuclears were not increased, nor were mast cells present, in the blood of the human and other subjects.

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**The Nature of the Tuberculin Reaction.**

*Karl Zieler, Ztschr., f. Immunitätsf. u. exper. Ther., 34: 240, Jena, May 11, 1922.*

This is a reply to the work of Selter, who also produced evidence that the tuberculin reaction is specific. Quotations from former works are cited to refute Sorgo's findings that focal reactions in the tuberculous can also be produced by diphtheria and dysentery toxin. The author maintains that the histologically characteristic changes of the tuberculous can be produced by tuberculins even after the exclusion of all bacillary elements, in fact even with dialysates, but never with other substances, like albumoses, liver extracts, etc. The specificity of these changes is also shown by the fact that after this subcutaneous administration of old tuberculin focal reactions may readily occur. These changes are of tuberculotoxic nature and occur only in human beings or animals infected with tuberculosis. Even if there are encapsulated or killed bacilli somewhere in the body, these give off substances into the circulation that give rise to allergic reaction of the cells of the body (experiments on rabbits with collodion sacs filled with Koch bacilli in the peritoneal cavity). Tuberculin hypersensitivity depends upon cellular properties. Immunity to tuberculosis and immunity to tuberculin are not identical.

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**The Physicochemical Action of Tuberculin on the Blood Measured by the Suspension Stability of the Erythrocytes and the Flocculating Capacity of the Plasma.**

*Wilhelm Starlinger, Ztschr. f. d. ges. exper. Med., 27: 305, Berlin, April 26, 1922.*

In 62 tuberculous and 37 nontuberculous persons the rapidity of sedimentation of the erythrocytes was tested by placing 0.2 c.c. 5% sodium citrate solution in a sedimentation glass and adding blood up to the first mark. The sedimentation at 6, 12 and 18 mm. was observed. Then the plasma was partially replaced by tuberculin and the inhibition of sedimentation observed. The average value at the 3 levels (6, 12 and 18 mm.) was called the sedimentation mean value (SMW). As the second sedimentation was slower than the first, by dividing  $SMW_1$  by  $SMW_2$  the relative inhibition quotient was obtained (RHQ). The division of the individual RHQ by the RHQ of the control gave the absolute quotient of inhibition (AHQ). These figures are comparable with one another. The flocculation reaction was carried out, equal parts of citrated plasma and saturated sodium chlorid solution being mixed. The results are summarized in 6 paragraphs.

(1) Tuberculin inhibits the sedimentation of erythrocytes considerably. The precipitate consists of glycerin, bouillon and tubercle bacilli. Glycerin and concentrated bouillon cause a stabilization of the

suspension, but the tuberculin acts more intensely than would be indicated by the sum of its constituents.

(2) The tuberculin was shaken up with kaolin, bolus and starch (by which its constituents of low dispersibility were removed) and then added to the plasma. It was found that the kaolin and bolus tuberculin causes a slight, and the starch tuberculin a considerable decrease of the inhibition of sedimentation as compared with the control tuberculin. This shows that the tuberculin by virtue of its highly dispersible products of catabolism can stabilize the plasma colloids.

(3) If the tuberculin is allowed to act for a longer time on the plasma, the inhibition of sedimentation continues to grow less, no matter whether the plasma comes from tuberculous or nontuberculous individuals.

(4) Great rapidity of sedimentation (and therefore low SMW) corresponds to a high AHQ. It is easy to explain this phenomenon. In rapid sedimentation only the intense inhibitory action of the tuberculin can take effect, but the weakening of this process, which was observed when the tuberculin acted on the plasma for a long time, is excluded.

(5) Other tuberculins, including the partigens of Deyke and Much, show the same action as old tuberculin, but the action of many of them is weaker than that of old tuberculin.

(6) Finally there is a greater retrogression in the inhibition of sedimentation on continued action of the tuberculin on the plasma, the more strongly the tuberculin has inhibited the sedimentation. The author explains this on the basis that the constituents of the plasma and the tuberculin combine to form a larger complex in which the reaction is not specific for the plasmas of tuberculous patients.

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#### **Further Researches on Detoxicated Vaccines.**

*David Thomson and Robert Thomson, Brit. M. J., London, May 20, 1922, p. 796.*

During the past year successful researches have produced more efficient detoxication. It is the authors' ambition to reach such an efficiency of detoxication that doses of one billion germs (1 c.c. of wet germ mass) may be inoculated at a time. Doubtless when such doses are attained the immunity created will produce remarkable curative results. In preventive medicine, by such massive inoculations, one may hope to guarantee a complete and certain immunity from a given disease for a considerable time. Experiments carried out on rabbits proved the importance of dosage in the stimulation of anti-substances to any foreign protein. Sheep red cells were injected. From these experiments it can be assumed that to obtain a highly potent antiserum in man, massive doses must be injected. For successful immunity it is not necessary to get severe toxic reactions. Sheep corpuscles are nontoxic, and the inoculations produced no toxic reactions whatsoever, yet there was an enormous immunity response. It was found that the detoxicated vaccines of a year ago were a mixture

of the nontoxic fractions and a small proportion of the unchanged toxic germs. This defect is now avoided by passing the solutions of each germ fraction through a Chamberland filter, before precipitating them. As the precipitates obtained are 10 times less toxic, this filtration has brought about a tenfold increase in the dosage. To remove the poisons residing within the germ bodies the latter must be entirely disintegrated or autolyzed. Heretofore, chemicals only were used, but mechanical means also are necessary. One of the authors has constructed a machine which has a cutting and grinding action upon the germ emulsions, so that now weaker chemicals can be used in dissolving the germs.

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**Virulence of the Organism as a Factor in the Efficacy of Prophylactic Vaccines.**

*W. F. Harvey and K. R. K. Iyengar, Indian J. M. Res., 9:730, Calcutta, April, 1922.*

Experiments were carried out on pigeons as to the efficacy of a fowl cholera antigen killed by heat, and injected intravenously at seven days' interval. The doses used were respectively 0.5 mg. and 1 mg. dried bacterial substance, as determined from Brown's tables (1919). The use of fowl cholera was decided on because it had the advantage of being pathogenic to pigeons, and so enabled authors to use the more convincing protection experiments in their trials. The main trial was that of protection afforded by a vaccine prepared from the same strain of organism in its virulent and its avirulent state against the inoculation intravenously of a series of test doses of the living organism in its virulent condition. The organism when originally obtained was very virulent. This virulence was maintained by continued subculture on rabbit blood agar, the avirulent strain being obtained by continued subculture for twelve months on ordinary nutrient agar. The avirulent strain killed only in doses of 1 mg.

In addition to the evidence given by the protection trials, there is that of the agglutination reaction obtained in a series of pigeons specially set apart for the purpose, and not used in the protection test. The method of recording the agglutination was that advocated by Harvey and the 2 dilution values were practically those of complete agglutination and of macroscopically evident flocculation respectively. Each of the pigeons that had been treated with a vaccine prepared from the virulent and the avirulent organism had its serum tested against both virulent and avirulent strains. The control trials were carried out on 20 pigeons and were designed to demonstrate the degree of virulence possessed by the organism used as test of protection, and also to give a basis for the conclusion that protection had been afforded. Of the 40 pigeons set apart for the vaccine trials, 15 in each category were used for the test of relative protection given by the vaccine prepared from the virulent and the avirulent organism, and 5 each for the agglutination results from the same 2 strains. In the control series 17 pigeons out of 20 succumbed to the doses, which were of a graded character. The dosage in this series ranged in both directions further than that in the series of pigeons receiving preliminary treatment

with vaccine. The authors conclude that the protection afforded by the avirulent strain bears the proportion in these trials to that afforded by the virulent strain of 9 lives saved out of 15, as against 10 lives saved out of 15. The difference shown between the 2 is slight, and may or may not be really in favor of the use of the virulent strain.

The response of inoculation of an avirulent strain in the shape of agglutinating power of the serum is the same both for the avirulent and the virulent strain. The same result holds good for the inoculation of a virulent strain.

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(1e—20)

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**Preservation of Forensic Serum and Antiserum with Yatren.**

*Georg Strassmann, Deutsch. med. Wchnschr., 48:487, Berlin, April 14, 1922.*

Hinz kept horse and dog serum sterile with 3% yatren. This serum did not produce any reactions which can be attributed to yatren. The author preserves serum or antiserum with yatren, 1-5 gm. of the powder being added to 100 c.c. serum. A yellow scum first forms upon the surface, and the undissolved mass of yatren sinks to the bottom as a yellow precipitate. The serum becomes dark brown in color, and remains clear for months and even years. By bacteriologic examination it is found sterile. For purposes of injection it is desirable to filter the serum. Biologically, the serum is not altered in the least. For the antiserum the addition of 1-2% of yatren should suffice. Regardless of temperature, and without special precautions, the serum may be preserved in ordinary glass utensils.

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**The Action of Proteins, Ferments, Toxins and Serums to Adsorption by Aluminum Hydroxid.**

*M. A. Rakusin, Ztschr. f. Immunitätsf. u. exper. Ther., 34:155, Jena, May 11, 1922.*

The infusion method was used, that is a certain amount of the dry substance to be examined was mixed with aluminum hydroxid in such amount as to make a 10% mixture. After standing in a flask for 24 hours the clear fluid was decanted and centrifuged and the concentration of the solution was determined (by steaming at 50° C.). The tabulated results indicate that only the casein is adsorbed by the aluminum hydroxid, whereas all the other substances are split; in chondrin there is evidence of transition from a chemical (hydrolytic) process to normal adsorption. The aluminum hydroxid manifests its amphoteric character toward the protein and seems peculiarly adapted as a remedy for adsorption of poisons in the intestine. The following percentages of adsorption products are obtained with the various substances: egg albumin, 19.22%; casein, the whole molecule is adsorbed; alphagelatin, 49.88% adsorption and splitting; betagelatin, 20.65% adsorption and splitting; chondrin (0.2%), 48.26%; chondrin (1.2%), the whole molecule is adsorbed; pepsin, 12.4%; diastase, 7.14%; old tuberculin, 4.44%; tuberculin Denys, 7.67% (only impur-

ities); tuberculin Louvain, 23.08%; spermin, 13.7%; antidiphtheritic serum, 43.77% (only added protein); pepsin febrin peptone, 24.19%.

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### **Production of Anti-Sheep Amboceptor in a Mule.**

*Ruth Gilbert, New York State J. Med., 22:286, June, 1922.*

It had been noticed that normal rabbits whose blood contained natural amboceptor, were usually satisfactory for the production of hemolysins. It was thought advisable, therefore, to have the serum from a number of normal mules and horses tested for natural anti-sheep amboceptor. Trial bleedings from 16 mules, 7 horses and 1 colt were tested for hemolysins and agglutinins for sheep red blood cells. The serum from 3 of the mules showed considerable hemolysis when tested undiluted, 1 specimen causing nearly complete hemolysis through 0.02 c.c. and another through 0.03 c.c. The serum of 1 of the horses contained a trace of amboceptor when tested undiluted. The serum from the colt contained a slight amount of amboceptor, partial hemolysis being obtained with 0.1 c.c. of undiluted serum. A trace of hemolysis was produced by the serum when diluted 1:10. The serum from these animals showed no agglutinins for sheep cells. The serum from 7 of the others (4 mules and 3 horses) did, however, contain agglutinins for these cells.

It was decided to immunize the mule whose serum showed hemolysis in 0.03 c.c. (the animal giving the slightly better reaction had diphtheria antitoxin in sufficient quantity to warrant its use for that purpose). Intravenous inoculations were made twice weekly. The first dose consisted of cells from 20 c.c. of sheep blood. The dosage was increased as rapidly as possible, but since, after the fifth dose, each inoculation produced a marked reaction in the mule, either at the time or soon after, 185 c.c. of packed cells was the largest amount that could be given. The best product was obtained by giving a few doses of sufficient size to induce a marked reaction. A series of 422 complement fixation tests for syphilis was made in duplicate, using amboceptor produced in rabbits and amboceptor from the mule. The results of 415 of these tests agreed exactly. Since May 16, 1921, the amboceptor from the mule has been used in all of the writer's routine tests, and has been found satisfactory in every respect.

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### **The Ether Sensitiveness of Antibodies.**

*J. Forssmann, Klin. Wchnschr., 1:1054, Berlin, May 20, 1922.*

If the substance causing the positive Wassermann reaction is precipitated with the euglobulins and this is treated at inactivation temperature with ether, this active substance is destroyed. Hemolysins are destroyed in the same way by the ether inactivation treatment, while agglutinins are not affected. The destructive action on the hemolysins is to be regarded as an adsorption process and the same explanation evidently holds also for the substance causing the Wassermann reaction.



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**Nonspecific Cross-Fixation of Complement with Wassermann and Tuberculosis Antigens.**

*Anna Dean Dulaney, Am. Rev. Tuberc., 6:192, May, 1922.*

This is a preliminary report on work done in the Public Health Laboratory of the University of Missouri, being based on a study of 600 cases. Of this number 100 serums were from known tuberculous cases, and 500 represented specimens of blood sent in for a routine Wassermann. The work was done with the hope of contributing data on the following questions: Do tuberculous, nonsyphilitic serums give positive Wassermann reactions? Do Wassermann-positive, nontuberculous serums give positive tuberculosis fixations?

Eight of the 100 serums from known tuberculous patients, who gave neither history nor clinical evidence of syphilis, yielded positive Wassermans with cholesterinized antigen; of these, 2 gave a 1+ fixation with alcoholic antigen. The others were negative. Of the 500 serums received for routine Wassermans, 23 giving positive Wassermans also gave fixations with tuberculosis antigen, while 20 Wassermann-negative serums gave positive tuberculosis complement fixations. The 23 serums giving fixations with both Wassermann and tuberculosis antigens, represented 3 active tuberculosis cases, 2 suspected tuberculosis cases, 15 persons with neither history nor clinical evidence of tuberculosis, and 3 cases of which no histories could be obtained. Of the 20 serums giving negative Wassermans but positive tuberculosis complement fixations, 7 were from active tuberculosis cases, 5 from suspected or treated syphilitic cases giving neither history nor evidence of tuberculosis, 7 from persons giving neither history nor evidence of tuberculosis, and 1 from a case where no history was obtained.

Of so-called normal persons, giving a positive Wassermann 10% also gave a fixation with tuberculosis antigen. Of so-called normal persons giving a negative Wassermann, 3% gave a fixation with tuberculosis antigen. Of the 500 sera 5% gave fixation with tuberculosis antigen when there was no history or clinical evidence of tuberculosis.

The results tend to show that a positive tuberculosis complement fixation in the great majority of cases indicates an active tuberculosis. In the case of so-called normal persons who give a fixation with tuberculosis antigen, there is always a possibility of an old or latent infection. The serums from known tuberculosis cases, giving positive Wassermans without history or clinical evidence of syphilis, are regarded as cases of nonspecific cross-fixation. When only a cholesterinized antigen is used, a positive Wassermann in active tuberculosis is not to be accepted without thorough investigation.

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**The Relationship of Lipoids and Proteins to Serum Reactions in Tuberculosis.**

*W. Ray Hodge and M. F. MacLennan, J. Immunol., 7:253, May, 1922.*

Experimental evidence indicates that the fixation bodies in human tuberculous serums are lipoidal in character because extractions of dried serums with alcohol, chloroform and ether remove these bodies almost

completely. In serums dried on filter paper and redissolved in saline there is only a moderate loss of fixation power, indicating that the active substances redissolve quite readily while protein does not readily redissolve after drying. The euglobulin fraction of the serum does not regularly contain fixation bodies, but they occur in the supernatant fluid in the same concentration as in untreated serum. There is also experimental evidence which indicates that the inhibitive bodies in human and certain animal serums are protein in character, as they are almost completely precipitated in the euglobulin fraction of the serum.

The inhibitive power of guinea-pig serum is not regularly increased following protracted anaphylactic shock when the unsaturated lipoids of the serum are increased. It is possible that cellular disruption not only increases the unsaturated lipoids (from the cell wall) in the serum but also occasionally the euglobulin. The inhibitive bodies are not removed by alcohol, chloroform and ether extraction of dried serum; serum however that is dried and redissolved in saline shows a marked loss of inhibitive power, indicating that the substances responsible for the inhibitive reaction are protein in character as the proteins of dried serum redissolve again only incompletely.

The identity of the substances responsible for the inhibitive reaction of Calmette and that of Caulfeild seems certain. Minor differences exist, but the authors have found that the active substance in Caulfeild's reaction is precipitated in the euglobin fraction; Calmette finds that the inhibitory substance in his hyperimmune serums is precipitated in the euglobulin fraction also. The authors found moreover that human serums showing a strong inhibitive reaction by Caulfeild's method also give a similar reaction by Calmette's method. The fact that the substance responsible for Caulfeild's reaction is increased when animals are immunized with tubercle bacillus, further identifies it with the substance responsible for Calmette's reaction. Calmette finds inhibitory substances in high concentration in the serum of hyperimmunized cows. The authors found that there is a moderate dose of Caulfeild's inhibitive substance in the serum of immunized rabbits and a more marked increase in the serum of immunized guinea-pigs.

The substances responsible for the inhibitive reaction of Caulfeild are contained almost wholly in the euglobulin fraction of the serum. It is concluded that the substances responsible for the inhibitory reaction of Calmette are identical with those responsible for the inhibitory reaction of Caulfeild.

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**The Behavior of Sheep Blood Immune Serum toward the Lipoids from Heterogenetic Organs. Antigenic Properties of Lipoids.**

*Kurt Meyer, Ztschr. f. Immunitätsf. u. exper. Ther., 34:235, Jena, May 11, 1922.*

Two sheep blood immune serums (diluted tenfold) were kept at 37° C. for an hour with an equal amount of 10% guinea-pig kidney emulsion. Hemolysis was started with the centrifuged decanted fluid. The titer was reduced to half in both serums by the binding with guinea-pig kidney, that is, the serums contained equal parts of isogenetic and heterogenetic sheep blood hemolysins.

The serums were mixed with 0.5 c.c. horse kidney cephalin (1:10,-  
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000) plus 0.5 c.c. guinea-pig complement; after an hour 0.5 c.c. doubly sensitized beef blood was added. The sheep blood immune serums showed complement fixation with the horse kidney lipoid.

By varying the experiments the author came to the conclusion that sheep blood immune serums, depending on their content of heterogenetic antibodies, enter into reaction with the acetone-insoluble lipoids from heterogenetic organs and that these lipoids bind the heterogenetic hemolysins.

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**The Increase of Hemagglutinin and the Stimulation of Hemagglutination in Human Serum.**

*Kurt Meyer, Ztschr. f. Immunitätsf. u. exper. Ther., 34: 229, Jena, May 11, 1922.*

In about 100,000 Wassermann tests the author found 8 serums which markedly agglutinated sheep erythrocytes. In one case there was a normal agglutinin of a particularly intensive action, so that the limit for rabbit blood (0.25 c.c. 5% suspension) was 0.002 c.c. serum. These agglutinins were destroyed only at 70°C. The serum showed no increased agglutinin effect toward bacteria. Two other serums agglutinated only sensitized blood; one of these, from a case of bronchitis, had the following properties: It agglutinated sensitized sheep erythrocytes in amounts of 0.001 c.c. and it increased the agglutinating power of a sheep blood immune serum twenty-fold. The intensity of this agglutination power increased with increased sensitization of the erythrocytes. Fractionization of the serum with CO<sub>2</sub> decreased the effectiveness by half and heating to 70°C. inactivated the serum. The agglutinating power of the serum was lost on shaking. If 0.1 c.c. of a 0.2% solution of cobra toxin was added to 0.5 c.c. serum the agglutination power disappeared. This fact, together with the thermolability, shows its identity with the so-called third component of the complement. Most likely the substance that promotes agglutination is of lipoid nature.

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**Hydrogen-Ion Studies. III. Hydrogen-Ion Changes in the Agglutination of Bacteria by Immune Serum.**

*Edwin F. Hirsch, J. Infect. Dis., 30: 651, June, 1922.*

Since many chemical reactions are accompanied by significant changes in the hydrogen-ion concentration of the medium in which they occur, it appears possible that a study of the hydrogen-ion concentration of the medium in which agglutination of bacteria by immune serum takes place may throw some light on the cause of such agglutination. Immune serums were prepared in rabbits. Bacterial suspensions were made with normal salt solution, diluted to a medium density, and then heated to 56°C., to kill the organisms. A number of dilutions of immune serum in salt solution were added to the suspensions, and the mixtures were incubated overnight at 37°C. The hydrogen-ion concentration of each was determined the next morning. It was found that bacteria suspended in normal salt solution behave chemically and electrically like the anion of the salt of a strong base and a weak acid, and that when bacteria are agglutinated by homologous immune serum, the alkalinity of the

medium in which the reaction occurs is increased. This change in reaction is believed to result from differences in the dissociation constants of the reacting substances and their products.

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**New Experiments on Isohemagglutinins.**

*Fritz Verzár, Klin. Wchnschr., 1: 929, Berlin, May 6, 1922.*

It is known that the blood serum of healthy humans often agglutinates the red cells of other persons, and that human beings may be divided into 4 groups on a basis of this isoagglutination: groups II and III which are agglutinative for each other, the former containing the peculiarity A and the latter, the peculiarity B; group I which agglutinates all the others and has both peculiarities A and B; and group IV which does not agglutinate and is called O. Peculiarity refers to the agglutinability.

The membership of the red cells to one blood group is formed even in the new-born and is not always the same as that of the mother. The formation of the specific agglutinins occurs during the first year of life and then remains constant for the remainder of that person's life. The group to which one belongs depends on the blood group of the parents. It is said that the group peculiarities A and B are inherited according to the Mendelian law but this can be demonstrated only by heredity through 2 generations.

Isohemagglutination may be used in forensic medicine. It is possible to say of some corpuscles that they do not belong to a certain individual if they are agglutinated by his own serum. The determination of the belonging of a blood to a certain blood group may be of importance.

Isohemagglutination is a peculiarity of a normal person and the cause of the various blood groups has no relation to disease or constitution. It is an expression of race peculiarity. Extensive examination on good human material of the Entente army showed that the biochemical race index, that is, the frequency of relation of all persons with peculiarity A to all persons with peculiarity B, is highest in the English and lowest in the Indians. The frequency of peculiarity A becomes less from the west and north to the east and south. It is most frequent in the English and Germans and most rare in the Indians and Senegalese. Peculiarity B shows the reverse condition. The race index for the English is 4.5, diminishes towards the east and south and reaches a value of 0.5 in the Indians.

Verzár examined 3 living races in Hungary in order to determine their membership to one blood group. The biochemical race index of the Hungarian is 1.66 and is very close to that of the Turk (1.8). This is explained by the 1200 year old relation between the two peoples, that is, between the Hungarian and the Ural-Altaic peoples to which the Turks also belong. The German colonists who settled in Hungary more than two hundred years ago show a striking frequency of the groups found in Germany. Peculiarity A is much more rare than peculiarity B in Gipsies and this is the reverse of all other European peoples. The index is 0.6 which is nearly the same as in Indians. Philology teaches that the Gipsies wandered in from India about the year 1200. The

frequency of a blood group in a race is an acceptable sign of that race. A and B are signs of 2 original races whose mixture must have occurred during a very old period of culture.

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**Auto-Agglutination of the Blood.**

*Leone Lattes, Haematologica, 3:101, Naples, March, 1922.*

It is generally admitted that in normal conditions auto-agglutination does not occur. However, several authors assert their belief in the possibility of the existence in man of this phenomenon; and Lattes deemed it of sufficient interest, even from a clinical point of view, to institute additional investigations on its nature and significance. The question of auto-agglutination must be studied anew fundamentally and systematically. A case is cited in which he made observations on the blood of a patient, and found auto-agglutination very marked. He attempts to establish the proper relationship between auto-agglutination, iso-agglutination, and agglutination in rouleaux. Auto-agglutination can be considered only as an exaggeration of the normal property of red cells of assuming the formation of rolls of coin; it depends exclusively on the blood serum, and not on the red cells, and has nothing at all in common with iso-agglutination.

From the point of view of forensic hematology, the possibility of auto-agglutination may interfere with the individual diagnosis of blood spots; hence a method is suggested for overcoming possible errors by testing an extract of the blood spot with suspensions of noniso-agglutinating red cells. Only when such test results negatively can the proper interpretation be put on the reactions obtained with the various species of iso-agglutinating red cells. If, on the other hand, the test is positive, the extract will have to be diluted until a negative result is obtained; then, in view of the enormous difference in titration between the 2 reactions, the specific reaction to true iso-agglutination will become evident and any opinion based on it will be of sufficient reliability.

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**Analysis of the Precipitation Phenomena by the Aid of the Anaphylactic Reaction with Reference to the Concurrence of the Antigens.**

*Martha Luginbuehl, Ztschr. f. Immunitätsf. u. exper. Ther., 34:246, Jena, May 11, 1922.*

If the products of precipitation are tested by the aid of anaphylaxis, it is seen that the antigen disappears from the reaction volume. To determine cause, experiments were undertaken with 2 mixtures: (A) 10 c.c. human serum plus 8 c.c. sodium chlorid and 2 c.c. antihuman serum from rabbits, and (B) the same as the foregoing, but normal rabbit serum instead of antihuman serum. After the onset of precipitation in A, the animals (guinea-pigs) were immunized with decreasing amounts and then human serum or rabbit serum was reinjected. As a result, the precipitation proceeded although the antigen became ineffective, and by a control test (B) the assumption of concurrence of



the antigens as the cause of the consumption of the antigen could be eliminated.

Guinea-pigs were passively immunized with 0.4 c.c. antihuman serum. The lethal dose for human serum was titrated on the animals and thereby the shock producing power of the residual fluid of the precipitate was compared with an immune precipitation. From the varying experiments it is evident that very different amounts of antigen are destroyed in the formation of the precipitate, depending upon the concentration of the antigen. The injected precipitate portions had absolutely no effect upon the prepared guinea-pig. From all the experiments the conclusion was drawn that the precipitinogen and precipitin are combined in the precipitate in such a way that they develop no antigenic effect, whereby the albuminoid of the immune serum remains absolutely intact.

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**Hydrogen-Ion Studies. VI. Hydrogen-Ion Changes on Precipitation of Human Serum by Immune Serum.**

*Edwin F. Hirsch, J. Infect. Dis., 30:666, June, 1922.*

Human serum and homologous immune rabbit serum were tested. Dilutions were made in clean sterile test tubes, and the reactions were determined after about eighteen hours, by the gas chain method. It was demonstrated that the precipitation of human serum by homologous immune serum is accompanied by an increase in the alkalinity of the medium similar to that observed on the agglutination of bacteria by immune serum and on the precipitation of colloidal gold by spinal fluid (Lange test). The phenomena may therefore, be regarded as chemically similar. The presence of an inorganic salt is as essential for precipitation in the precipitin test as for the agglutination of bacteria by homologous immune serum. The mutual precipitation of colloids bearing opposite electrical charges is generally known, and the laws governing it are thought to apply equally well to the precipitin reaction. The increase of hydroxyl ions on the precipitation of human serum by homologous immune serum probably results from a liberation of the sodium base whose dissociation constant is greater than that of the immune substance.

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**Hydrogen-Ion Studies. IV. Changes in Reaction Accompanying the Precipitation of Colloidal Gold by Spinal Fluid (Lange Test).**

*Edwin F. Hirsch, J. Infect. Dis., 30:658, June, 1922.*

In the colloidal gold test (Lange) with spinal fluid, the results are expressed in color changes from the pink red of the prepared colloidal gold suspension, the changes being plotted in graphs or expressed in numbers. The color of the suspension depends on the dispersion of the finely divided gold particles, and an increase in the size of the aggregates accompanies the changes in color. Since the particles of colloidal gold carry negative electric charges, as do bacteria suspended in dilute salt solution, experiments were carried out to determine whether their precipitation was accompanied by changes in the reaction of the medium

similar to those in the agglutination of bacteria by homologous immune serum. Mixtures of spinal fluid and gold solution were allowed to stand at room temperature overnight and their reactions were determined the next morning by the gas chain method. It was demonstrated that the agglutination of the gold particles as manifested by color changes, turbidity, or complete precipitation is accompanied by a parallel increase in the alkalinity of the medium. This change in reaction is similar to that observed in the agglutination of bacteria by homologous immune serum. The precipitation of the colloidal gold particles appears to depend on the presence of positively charged ions in the spinal fluid, probably protein substances.

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**Determination of the Quantity of the Blood by the Optical Method. Study of the Quantity of Blood in Some Cases of Nephritis.**

*G. Moscati and G. Napoletano, Riforma med., 38:435, Naples, May 8, 1922.*

The method proposed is founded on the fact that if we make a dilution of a determined optically active body, of which the degree of deviation is known, with the same liquid in which it is dissolved we shall be able to calculate the degree of dilution from the degree of optical deviation resulting. We determine the angle of deviation of the plasma of a living animal and then inject in the circulating current of this animal a carefully measured quantity of solution of a substance of strong rotatory power, having first determined the angle of deviation of such solution. After getting a complete mixing, we compute the new deviation of the plasma. Knowing the total quantity of the plasma, we arrive at the total quantity of blood, from the relationship between the plasma and the number of red corpuscles.

Abderhalden and Schmid used dextrine as an optically active substance; the writers, after long experimentation, adopted glucose. Their experiments established above all that glucose introduced does not become fixed with the red corpuscles, that with prolonged sojourn of the glucose there was less destruction of glucose than of dextrine and that the plasma did not alter the specific deviation of the glucose dissolved in water. To determine the rotatory power, the blood should be obtained within at least the first five minutes after the injection.

The above method was applied in experimental nephritis brought about in dogs with subcutaneous injections of small quantities of uranium acetate, and the writers noted that apart from the blood pressure, there was in fact a constant spontaneous hydremic plethora, through effective increase in the volume of the blood and particularly of the plasma in the experimental nephritic states, accompanied by striking albuminuria. This permanent plethora occurs in spite of the mechanisms that lower the transitory plethoric states, such as edema and transudation. It is not to be confounded with the transitory plethora from injections of liquid or concomitant lesions of the kidneys artificially produced. It has never till now, according to the writers, been demonstrated experimentally in renal diseases, because of insufficiency of methods.

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### The Composition of Normal Human Blood.

*V. Bie and P. Möller, Arch. d. mal. du coeur, 15:177, Paris, April, 1922.*

Volumetric studies of the blood have been incomplete. The authors have determined normal figures referring to the dry residue yielded by total blood and serum, the volume of red cells in defibrinated blood, the number of red cells and the hemoglobin, using 10 men and 10 women as subjects. They were all healthy, aged about 25 years, their hygiene was good and blood pressure normal; they were physicians, medical students or nurses. All tests were carefully checked. Tabulations showed that the average dry residue yielded by men's whole blood was 20.89%; by women's blood, 18.99%. The difference between the blood of the two sexes was thus 10% of the average. The difference between the maximum and minimum dry residue of the total blood for men was 1.90%, for women, 1.745%. The average dry residue yielded by the serum of men's blood was 9.01%; by that of women, 8.77%. The difference for the sexes was so slight (0.24%) that their serums may be considered equivalent in this respect, save as future studies may show that the difference is constant. The dry residue derived from serum was nearly constant in healthy individuals. Variations in the composition of the blood depended on the dry residue yielded by the red cells, the relation between the volume of the cells and that of the plasma and on differences of these 2 factors in the 2 sexes or in different individuals of the same sex. The figures for oxygen absorption proved to be, for men, 19.8%; for women, 17.85%. The hemoglobin for men was 14.75%; for women, 13.3%. The red cells were counted with the Thoma-Zeiss chamber and pipet, the blood being diluted with Hayem's solution, and an average of 5 counts being made per subject. The average normal number of red cells per cu. mm. in men proved to be 5,500,000; in women, 4,750,000. For men, the normal minimum was about 4,750,000, the maximum 6,500,000. For women the corresponding figures were 4,000,000 and 5,500,000. The normal range in men was 1,405,000; in women, 966,000. For obtaining the volume of red cells in defibrinated blood, the blood was agitated with glass beads. The defibrinated blood was then aspirated into glass tubes whose lumen was about 1 mm. in diameter and whose length was 5 cm., graduated in 100 divisions; the blood was then centrifuged. The average volume of red cells, for men, was 46.4%; for women, 38.7%. Of the dry residue contained in men's whole blood, 4.823 parts per 100 were derived from the serum, 16.067 from the red cells (total, 20.89). Of the residue of women's total blood, 5.375 parts were yielded by the serum, 13.613 by the red cells (total, 18.99). The larger quantity of dry residue, and the greater capacity for oxygen absorption, present in men's blood were due to a greater percentage of red cells. The slight differences occurring between healthy individuals of the same sex were likewise due to the volumes of the red cells.

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**Studies on Experimental Plethora in Dogs and Rabbits.**

*Edward B. Krumbhaar and Alfred Chanutin, J. Exper. Med., 35:847, June 1, 1922.*

The functional changes produced on the blood-destroying and blood-forming apparatus of normal and splenectomized dogs and rabbits by repeated transfusions of blood were studied, as well as the anemia which developed despite continued blood transfusions in 2 dogs splenectomized during plethora. A study of the effect of splenectomy on artificial plethora, and an attempt to find evidence of increased enzyme action in the spleens removed while the blood was being destroyed in greatly increased quantity, threw no light on the relation of the spleen to blood formation and destruction.

The decrease or absence of reticulocytes from the blood stream during plethora and their increase during plethoric anemia appears to be due to depression and activation of bone-marrow activity. The bone-marrow does not respond immediately upon the onset of anemia, but only after several days. Studies of the blood volume emphasized the constancy of plasma volume and the adaptability of the circulatory system to large increases in total blood volume. The destruction and elimination of blood cells, as measured by urobilin excretion, were greatly increased during the stage of plethora, and still more so during plethoric anemia.

After intravenous introductions of large quantities of nitrogen in the form of whole blood, the total nitrogen, urea, and ammonia in the urine and feces were not raised appreciably for some time after the onset of plethora, the normal organism being able apparently to store large quantities of blood or its decomposition products. With the onset of a plethoric anemia, urinary total nitrogen and urea excretion increase; albuminuria is also found at this time. The spleen, liver, lymph-nodes, and bone-marrow show the deposition of large quantities of blood-pigment, chiefly in the form of hemosiderin, usually occurring in phagocytes, though in late stages in large extracellular masses. Increased pigment deposition occurs even several months after transfusions. Phagocytes containing erythrocytes are found rarely, if at all, and only in the acute cases.

The removal of the spleen in dogs causes an increased tendency toward plethoric anemia, although a direct connection between the 2 was not established. In rabbits, whose spleens constitute only 0.05% of body weight, the production of plethoric anemia is more easy. The extra work caused by the absence of the spleen is taken over largely by the liver, although lymph-nodes and bone-marrow apparently have a share.

In rabbits the blood-pigment is deposited in the hemopoietic organs in large amounts, but under the conditions of these experiments, early fatal intravascular agglutination and thrombosis occurred and the results were unsatisfactory. As in human hemochromatosis, the pigment occurs in 2 forms; hemosiderin granules, and smaller, dark spicules, not reacting to the usual iron stains (probably hemofuscin). The latter pigment is also found seeded through the cells of the liver parenchyma.

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**Nephelometric Studies on the Influence of Temperature Increase on Serum and Plasma.**

*Ushinosuke Kiyotaki, Biochem. Ztschr., 128:354, Berlin, March 28, 1922.*

Heat-coagulation is the most familiar alteration of an albumin solution exposed to increased temperature. This change in dispersion is of interest in the study of immunity because clouding is referable to an alteration in globulin and is related to abolition of complement action. A new apparatus, Kleinmann's nephelometer, was employed for estimating alterations in dispersity. In the experiments the ratios of the readings obtained with the standard and experimental solutions are calculated from the following formula, which is designated as the clouding index:  $X=1_s \div 1_x$ . The clouding standard employed by the institute for its colloidal researches was adopted as the standard clouding and is one produced by a 1/200 molecular solution of  $\text{BaSO}_4$ . Bovine serum and plasma formed the experimental material, in addition to human serum and umbilical cord blood plasma. The blood was collected under aseptic precautions in properly sterilized vessels. Plasma was obtained by adding potassium citrate. The serum was warmed in Ostwald's water-bath. Ten readings were taken of each sample and the average determined.

The following conclusions are drawn from the experimental results: (1) Serum and plasma undergo alteration on warming that is accurately demonstrable by the nephelometer. Increased clouding of serum is due chiefly to globulin, though clouding of albumin likewise increases. (2) Increase in clouding occurs with duration of warming, the curve becoming more steep with increasing temperature. In some temperature zones the rise is steeper initially, but the curve shows no tendency to become rectilinear in the course of time, nor to attain constant clouding. Even with prolonged warming at low temperature (42-45° C.) clouding seems to increase slowly and permanently. (3) On comparing the velocity of clouding in serum and plasma it is found to be much higher in the latter near the coagulation temperature (45-46° C.). At a lower temperature (40-44° C.) plasma reacts more slowly and usually no visible alteration is observed. (4) Experiments show that clouding sets in as low as at fever temperature (39-42° C.). This fact seems to express delicate alterations in the condition of body protein in the clinical febrile condition. (5) Warmed serum with distinct changes in its dispersion shows no difference from normal serum in its behavior toward fresh guinea-pig serum complement. (6) Ultramicroscopic examination shows no difference between warmed and fresh serum. Both are optically almost clear, with sparse submicroscopic particles. (7) Clouding diminishes on diluting serum with physiologic sodium chlorid solution or Ringer solution. Alteration of clouding in serum and plasma under increasing temperature may be followed accurately with Kleinmann's nephelometer. Its theoretic and clinical utilization remains to be effected, especially in regard to alterations in serum during fever persisting several weeks.



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**Determination of Plasma and Hemoglobin Volumes After Unit Hemorrhages under Controlled Experimental Conditions.**

*E. B. Carrier, F. W. Lee and G. H. Whipple, Am. J. Physiol, 61: 138, June 1, 1922.*

Using methods previously described and controlled as to accuracy the authors made simultaneous plasma volume and hemoglobin volume determinations in dogs. The animals were fasted for 24 hours preceding the hemorrhage which was produced by means of a hypodermic needle introduced into the jugular vein, the blood being aspirated into a flask containing isotonic oxalate solution. This blood was then measured and its hematocrit value determined. If simultaneous determinations of plasma volume and hemoglobin red cell volume be done immediately after a unit hemorrhage, a striking similarity will be observed between the measured and the calculated values. The authors' tabulated results show such similarity.

To determine the blood volume values during certain periods of fluid intake and vigorous exercise the authors used the animals employed in the experiments reported in the previous paper. It was found that copious water ingestion caused a distinct rise in total blood plasma volume in the dogs, the authors reporting an average increase of 16 per cent. Sugar solutions by mouth do not influence the blood plasma which remains a constant. Short period of vigorous exercise did not modify the blood plasma volume to a convincing degree.

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**The Influence of the Electric Charge on Blood Viscosity.**

*Klothilde Meier, Biochem. Ztschr., 128: 508, Berlin, March 28, 1922.*

As the internal friction of colloids depends on different factors it seemed difficult to determine viscosity changes of whole blood with a varying hydrogen exponent. Nevertheless this is possible, although the blood contains electrolytes in large number in addition to various colloids, if the composition is kept quite constant and only one factor, i e. the H-ion concentration, undergoes precisely measurable variation. By titrating defibrinated venous human blood with carbonic acid the hydrogen exponent was varied as desired and then calculated according to Hasselbalch's directions from the amount of free and combined carbonic acid in the blood and the dissociation constants of carbonic acid. To determine internal friction Ostwald's viscosimeter was employed. In order to maintain, during the viscosity measurements, the H-ion concentration that had been previously imparted to the blood, toluol was placed above the blood in the viscosimeter to prevent carbonic acid being given off. Friction was measured in the thermostat at 20° C. Only the duration of flow was determined; the friction coefficient was not measured. Experiments were carried out with hemolyzed blood, hemolysis being effected with saponin. With the H-ion concentration prevailing in the body the hemoglobin molecule is charged negatively, the charge being derived from the ions adsorbed at the surface. A more alkaline reaction will increase this negative charge while an increas-

ing acidity is diminished by absorption of positive ions into the surface of this charge. This process of discharge proceeds with the occurrence of a sudden inconstancy at an experimental temperature of 20° C. and with a hydrogen exponent of  $\text{pH} = 6.86$ . Further viscosity measurements were undertaken with human erythrocytes suspended in physiologic sodium chlorid solution. The hydrogen exponent at 20° was  $\text{pH} = 6.55$ . Experiments were also conducted on whole blood. The researches show that hemoglobin and the plasma membrane of the colloids exhibit their minimum viscosity in an uncharged state, which is shown by the inconstancy of the carbon dioxid combination curve. With increasing H-ion concentration the internal friction of these colloids is first altered gradually, then inconstantly and their charge is correspondingly altered by stages. In whole blood the hydration of the blood-corpuscles diminishes with increasing H-ion concentration.

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**Note on a Possible Source of Error in the Bell-Doisy Method for the Determination of Phosphates in Blood-Plasma.**

*W. Denis and L. von Meysenbug, J. Biol. Chem., 52: 1, May, 1922.*

The authors found that when the Bell-Doisy method for the estimation of inorganic phosphates was applied to plasmas, both citrated and oxalated, anomalous results were obtained, particularly regarding color development. An investigation of the possible causes of this phenomenon led them to believe that this failure of color development is due to the presence of an excess of oxalate or citrate in the plasma. For work with horse or human-adult plasma the authors used 10 c.c. trichloroacetic acid filtrate (dilution 1:10), 2 c.c. molybdate reagent, and 2 c.c. hydroquinon solution of double strength (40 gm. per 1000 c.c.). With horse plasma, either citrated or oxalated, they were able by this procedure to obtain figures identical with those given for serum with plasmas containing as high as 20 mg. sodium citrate or 25 mg. potassium oxalate per 10 c.c. blood. The presence of amounts of anticoagulant greater than this invariably gave values for inorganic phosphate lower than those obtained on the serum of the same animal. The authors deem it desirable whenever possible to make determination of inorganic phosphates only on serum, and where plasma must be used, to restrict the amount of oxalate or citrate, and increase the quantities of molybdic acid and hydroquinon as described above.

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**Blood Sugars.**

*C. E. Brunton, Irish J. Med. Sc., 5: 57, April, 1922.*

The subject is discussed in 4 sections: the quality of blood sugars, their sources, their fate, and the quantitative estimation of blood sugar. Brunton was unable to obtain any original articles on the quality of sugars found in the blood. Standard text-books on physiology agree that glucose, fructose and galactose may all be found in the circulation, that mannose can be assimilated if administered, and that all these may be utilized in the body. The figures given in this paper represent the

amounts of blood sugars estimated as glucose. Sources of blood sugar may be grouped under 3 headings: carbohydrates of the diet after their hydrolysis by the enzymes of the alimentary tract, the stored carbohydrates of the organism, and the carbohydrates of nucleoprotein metabolism. There exists normally a balance between the carbohydrate store and supply, excess sugar being removed either by polysaccharid formation or by renal excretion, and deficiency being remedied by fresh supplies from the alimentary tract or from the glycogen stores of the organism. Of special significance in metabolism is the sugar assimilation limit. In considering the fate of blood sugar, if we assume that the muscles have power to form polysaccharid, then part of the blood sugar is removed in that way and the blood sugar as a whole disappears in 3 ways: by storage as polysaccharid, by direct use as a source of energy, either (a) in the muscles, (b) in the formation of proteins, or (c) in the oxidation of fats; and by excretion through the kidneys. The writer found 0.89-1.15% sugar in normal blood. In normal individuals the blood-sugar value rises to about 0.15% one hour after meals and returns to normal after two hours. Pathologic metabolic conditions greatly alter this curve. It may be said that, from the point of view of further research, MacLean's method for blood sugar estimation, by its superior accuracy combined with its comparative simplicity, promises to be a valuable aid in solving the problems of abnormal carbohydrate metabolism. The small concentrations of sugar in blood reflect the difficulty of estimating accurately its amount.

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**Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma.**

*W. R. Bloor, K. F. Pelkan and D. M. Allen, J. Biol. Chem., 52: 191, May, 1922.*

The lipid substances may be satisfactorily extracted from blood plasma by treatment with excess of hot alcohol-ether. In these extracts the fatty acid constituents of the lipoids may be separated from the cholesterol by saponification of the extract and extraction of the saponification residue with cold chloroform, which extracts the cholesterol, leaving the fatty acids (soaps) behind. These may be extracted from the residue by hot alcohol. Determination of the cholesterol is made on the chloroform extract after suitable concentration, by the Liebermann-Burchard reaction. The residue after extraction with chloroform is treated with boiling alcohol for the extraction of the fatty acids (in the form of soaps) in the following way: 10 c.c. of redistilled alcohol are added to each flask, the mixture is raised to boiling on an electric stove and kept boiling gently for a period of ten minutes. The hot alcohol is then poured through the small hardened filter which was used in filtering the chloroform into a 100 c.c. Erlenmeyer flask. The extraction with alcohol is repeated once, using 5 c.c. of alcohol, the hot extracting fluid being poured through the filter into the flask. The combined filtrates are evaporated to about 3 c.c., then transferred quantitatively to a small, graduated, glass-stoppered cylinder, and the flask is rinsed out with just enough alcohol to bring the volume in the cylinder up to 5 c.c. Then 100 c.c. of distilled water are measured into

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a 200 c.c. beaker and the alcoholic extract of the fatty acid is added with stirring through a small funnel with the stem drawn out to form an opening about 1 mm. in diameter and extending nearly to the bottom of the beaker. The cylinder is rinsed once with the solution in the beaker and the rinsings are poured back into the beaker through the funnel. To another beaker containing 100 c.c. of water are added through a pipet with stirring 5 c.c. of the alcoholic standard containing 2 mg. of a mixture of oleic and palmitic acids containing 60% oleic and 40% palmitic acids in 95% alcohol (redistilled). Then 10 c.c. of dilute hydrochloric acid (1 part concentrated acid, 3 parts water) are added to each beaker with stirring, and after standing not less than three or more than ten minutes the solutions are compared in the nephelometer, using the modified nephelometer from the Duboscq colorimeter. Since nephelometer tubes filled with the same solution rarely give the same readings on the two sides of the instrument the standard must be adjusted before readings are made. This is done by filling both tubes with the standard solution and inserting into the instrument, after which the jacket on the right is set at 30 mm. and the jacket on the left adjusted until the two light fields are equal. This point gives the equivalent of 30 mm. on the right side and calculations are made on this basis. The tube on the right is then filled with the solution to be tested and readings are made. Accurate determinations cannot be made if the standard and test solutions are more than 30% apart.

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### **The Pathochemistry of the Blood Lipoids in Experimental Anemia.**

*H. Jastrowitz, Ztschr. f. d. ges. exper. Med., 27: 276, Berlin, April 26, 1922.*

Rabbits were given fat-poor food and rendered anemic either by blood toxins (pyrogallol, pyrocin, nitrobenzol, glycocholic acid, staphylococci) or by blood-letting. The heart blood was examined for phosphatids by Bang's method, and for free and combined cholesterol, fatty acids and total fat, the plasma and erythrocytes being examined separately. There was an increase in the lipoids in the blood and plasma in anemia. In anemia from blood-letting the erythrocytes were richer in phosphatids, while the cholesterol was not always increased. Similar results, though not so constant, were found in hemolytic anemias, but they were dependent on the supply of the different lipid substances in the body. In chronic anemias which lead to exhaustion there must finally be a fall of lipoids in the plasma and erythrocytes, in which the phosphatids sink much more rapidly and intensely than the cholesterol, which continues to be ingested with the food. In acute intoxications there is increase of the phosphatids, especially in the erythrocytes. In intensive intoxication with pyrogallol the lecithin increases to a high degree in the plasma while it sinks in the erythrocytes. In subcutaneous pyrogallol and pyrocin intoxication a hypalbuminosis with increase of the lipid substance in the dry substance of the plasma was observed as a sign of a deconstitution on hemolysis. The lipid anemia observed in anemia in animals that have been fed on a fat-poor diet is independent of the fat phanerosis of parenchymatous organs.

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**The Physical Principles of a Rational Method for the Determination of the Coagulation Time of Venous Blood.**

*Edgar Wöhlisch, Ztschr. f. d. ges. exper. Med., 27:61, Berlin, March 25, 1922.*

Wöhlisch makes a distinction between two conceptions: the reaction time (RZ), that is the time from the taking of the blood until it begins to coagulate, and the coagulation time (GZ) the time until the completion of coagulation. The RZ is ordinarily determined by Bürker's method. A drop of blood is put in a damp chamber with as constant a temperature as possible and every half minute a glass rod is passed through to see if fibrin adheres to the rod. Wöhlisch is convinced, in opposition to the opinion of Morawitz, that only two factors are especially important: the temperature and mechanical manipulation of the blood. The amount of blood and the form of the surface on which it lies have no effect on the determination of the RZ by Bürker's method. The most useful method for the determination of the GZ is that of Morawitz and Bierich: 5 c.c. of venous blood is put in the pan of a scale and every two minutes it is tipped and is observed to see when, with the greatest possible constancy of temperature, the surface of the blood no longer follows the tipping. Fonio used smaller amounts of blood at room temperature and used watch crystals instead of scale pans. Bürker's method is sufficient for orientation at the bedside.

Wöhlisch studied the individual factors that may give rise to sources of error in determining the GZ. All conditions of the experiment were given in measurable data: (1) Correct measurement of the amount of blood is very important in determining the GZ. It is best done by counting drops, and in doing so attention must be paid to the position of the needle in space. If it is vertical 64 drops make a c.c., if it is horizontal 31. (2) As to the constancy of the GZ it is to be noted that only the blood coming from one puncture is to be considered. The coagulation time of individual portions is about the same as long as the blood flows freely. When it becomes difficult to fill the syringe the GZ is often considerably shortened counting from the moment the syringe is filled. (3) The form of the vessel used also has an effect. The flatter the surface the greater the distribution of the blood; therefore the conditions for fibrin formation are more favorable and the GZ shorter or even the same as the RZ. Wöhlisch uses spectacle glasses of —10.0 diopters. Increasing curvature of the glass increases the GZ. It is of practical importance that with flat glasses the form of the surface of the blood is irregular; with concave glasses the surface is round, and this is attained with glasses of —10.0 diopters. Parallel determinations agree best when glasses of —10.0 diopters are used. (4) Frequent moving of the blood shortens the coagulation time. The glass should be tipped at regular intervals by the clock and care taken to make the excursions of the same amplitude each time. (5) A coagulation thermostat, said to exclude the effect of temperature, is a blood chamber with double walls, a window, incandescent light for heating and a small pedestal for the glass which can be tipped from outside with a rod. In the Petri dish in which the glass lies there is moist cellulose. (6) In carrying out his experiments Wöhlisch uses

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the above apparatus and puts 0.75 to 1 c.c. of blood at the lowest point in the glasses. All precautions are taken. The glass is tipped once a minute. The time when the surface no longer moves is regarded as the end point of coagulation. (7) The limits of error are about 20%. By observing all the above-mentioned precautions the error in using blood of constant characteristics is about 6%. Those errors which are caused by changes in the chemicophysical characteristics of the blood due to the manner of taking it lie without the scope of this article.

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**Obtaining a Coagulation Ferment from the Blood Serum.**

*Max Bleibtreu, Pflüger's Arch. f. d. ges. Physiol., 194:318, Berlin, March 31, 1922.*

Atzler and Bleibtreu have described a method of obtaining a durable coagulation ferment, in which the thrombin or metathrombin is absorbed by casein and then kept in an alcoholic solution ( $\frac{1}{3}$  to  $\frac{1}{4}$  volume alcohol). The alcohol content guarantees the sterility of the solution and seems also to shorten the coagulation time, but produces a clot that is much less firm than that produced by normal coagulation. It is therefore recommended that the alcohol be evaporated again by means of a water column or rotation pump; it is then concentrated to about two-thirds of its original volume at a temperature of not over 40° C., a vessel cooled with ice being inserted between the pump and the evaporating vessel. The alcohol content is greatly decreased in this way, but is not entirely abolished. Such ferment solutions cause a rapid coagulation with a firm clot. Though alcohol alone brings about a certain degree of coagulation, yet control experiments with casein treated with alcohol without the addition of the coagulating ferment showed the fermentative nature of the coagulation observed. Also the solution poorer in alcohol retains its effectiveness for a longer time, especially if it is kept in the cold, but later its effectiveness gradually decreases as a result of bacterial decomposition. If the solution is shaken up with chloroform and left standing under a layer of chloroform, it remains effective for several weeks.

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**A Blood Anticoagulant Obtained from Body Tissue; Its Chemical Nature and Its Manner of Action.**

*C. A. Mills, George Mynchenberg, George M. Guest and Stanley Dorst, Am. J. Physiol., 61:42, June 1, 1922.*

These authors, in a recent work on "tissue fibrinogen" and its action in blood clotting, noted that the protein fraction of the "tissue fibrinogen" when taken alone acted as a very active anticoagulant. In this paper they describe the method of its preparation, its chemical nature and its manner of action in rendering the blood noncoagulable both in vivo and in vitro. The anticoagulant action of the protein fraction of tissue fibrinogen is probably due entirely to its great phospholipin combining power, by virtue of which it attaches to the free end of the cephalin molecules of the tissue fibrinogen; thus leaving no

point for union to the blood fibrinogen through calcium. The method of preparation consisted of thorough benzene extraction of dried and powdered lung tissue (calf and horse lungs were principally used) at room temperature for several days, or until the benzene filtered off perfectly clear and colorless. This procedure transformed the coagulant of such lung tissue into a strong anticoagulant, which may be made still more active by addition of small amounts of acid to precipitate any tissue fibrinogen molecules that still retain phospholipin. Thus, whereas the acid precipitate from an active coagulant extract of fresh calf lung contains 41.6% phospholipin, the acid precipitate from one anticoagulant extract contained only about 13% phospholipin, and the anticoagulant globulin remaining in solution after the acid precipitation contained only 0.34% phospholipin. This final globulin, almost phospholipin-free, was obtained by half saturating the solution with ammonium sulphate, since addition of acid sufficient to precipitate it seemed greatly to reduce its anticoagulative activity. The authors were able to prepare an even stronger anticoagulant from liver than from lung by benzene extraction.

Discussing the chemical nature of the tissue fibrinogen the authors found its probable composition to be a protein molecule containing no phosphorous and having a nitrogen content of about 16%, to which are attached about 13 molecules of a phospholipin, presumably cephalin. This compound has a capacity for union with cephalin, evidenced by the fourfold increase in its coagulative activity on saturating it with cephalin. As its phospholipin is removed by benzene extraction it rapidly loses its coagulative action and soon becomes a strong blood anticoagulant. The anticoagulant globulin is capable of uniting with the free bond of the tissue fibrinogen phospholipin and thus reducing its coagulative activity. Almost half the phospholipin of tissue fibrinogen was found to be thus united with and rendered nonextractable by lipid solvents (boiling alcohol and ether).

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#### **Quantitative Determination of Thrombin in the Serum.**

*Edgar Wöhlisch and Conrad Pieritz, Ztschr. f. d. ges. exper. Med., 27: 82, Berlin, March 25, 1922.*

A simple method for the quantitative determination of thrombin, that ferment which transforms fibrinogen into fibrin, was devised by Stephan: He ascertains the increase in rapidity of coagulation that is brought about by the addition of a certain amount of serum to a fresh control blood. He also determines the coagulation time (GZ) of one c.c. blood with nothing added to it and then after the addition of 0.05 c.c. of the serum to be examined to 1 c.c. of this same blood. He calls the quotient of the two values the coagulation-hastening factor (GBF). Normally this should vary between 1.4 and 1.8. After irradiation of the spleen he found a decrease in GZ and an increase in GBF. Wöhlisch and Pieritz found that in hemophilia the GBF remains the same and is influenced by Roentgen rays in the same way as in normal subjects. They then made a study to determine whether the factors found in their earlier work to be important in the determination of GZ were

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also of value in determining GBF. So far as the movement of the glasses containing the blood is concerned, the tipping, which is after all only a more or less relative movement of the blood, must be of greater importance in the unmixed blood, than in the blood to which serum has been added, as the latter is naturally well mixed with thrombin already. Therefore theoretically the GBF would be smaller if the glass were moved frequently. This was found to be actually true. But the GBF is independent of the form and curvature of the glasses. The results of the experiments with reference to temperature were not uniform. On using blood from different patients GBF values were found, all of which were larger than the constant value given by Stephan. And in the use of 2 control bloods for determining a serum there were considerable differences. Moreover it should be noted that the end-point of coagulation cannot be determined with absolute accuracy. The author has therefore developed a new method which measures the reaction time (RZ) as it occurs in hemolyzed blood. A definite amount of blood measured in drops is placed in glasses of uniform caliber which contain a measured amount of distilled water. A glass rod is used at certain intervals to stir them, all the glasses being stirred the same length of time. In examining a serum a measured amount of it is taken and added to the hemolyzed blood. The glasses in which it is put are examined every minute in transmitted light from a strong source of light. The beginning of coagulation is manifested very definitely by a sudden turbidity, which is no less defined in the tubes with serum added. Quantitatively there is not a direct proportion between the rapidity of coagulation and the amount of serum added; the rapidity of coagulation increases more slowly. The values are parallel with those obtained by Stephan but are more reliable.

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## **Fibrinolysis. II.**

*Max Rosenmann, Biochem. Ztschr., 128: 375, Berlin, March 28, 1922.*

If various fibrins are prepared with different amounts of calcium it is found that the resistance of normal amounts of calcium does not lie where coagulation first takes place but at about one-half of the calculated higher calcium values. As natural leukocytic fibrin is subject to autolysis after two or three days the fibrin employed for the experiments was conserved in 25% alcohol. The fibrinolytic substance thrombolysin was purified by successive precipitation with alcohol, ammonium sulphate and zinc chlorid. Thrombolysin is not dialyzable. Its activity is most favorable at 37° C. Temperatures of 46°-48° C. injure it. With acid, alkaline and neutral reactions it is coagulated to form a gelatinous mass. Under certain conditions, for instance, in the presence of salts and in a certain dilution, no coagulation, but precipitation takes place. The gelatinous mass is soluble in excess acid. The optimum activity of thrombolysin is obtained with a neutral reaction. With the same amounts of fibrin and thrombolysin, fibrinolytic velocity is directly proportional to the amount of thrombolysin. Human fibrin behaves toward thrombolysin exactly like horse fibrin, so that all results ob-

tained with the latter are valid for human fibrin. Tuberculous exudate retards fibrinolysis very markedly but does not arrest it if sufficient thrombolysin is added. Coagulation is also retarded or arrested by excess calcium, which is in agreement with E. Freund's observations. A slight excess of calcium salts diminishes the elasticity of fibrin coagulum and no retraction takes place. Slight calcium increase causes the coagulum to become more voluminous and to be subject more readily to autolysis. Fibrin inactivated at 45° and 50° C. is less resistant than that kept in 25% alcohol. A temperature of 57°-62° C. alters the physical properties of fibrin and renders it insoluble in salt solutions or by thrombolysin. It is practically unaltered by 25% alcohol so that it may be employed as indicator in autolytic experiments. The autolysate of human fibrin was shown to contain a ferment having the character of thrombolysin.

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**Study of the Osmotic Condition of the Blood-Cells.**

*Rich. Ege, Klin. Wchnschr., 1:997, Berlin, May 13, 1922.*

If the volume of the blood-cell is a result of the function of osmotic pressure of the fluid, then volume changes must follow the laws of osmosis quantitatively. That this is not true is due to the considerable dispersible phase of the blood-cell, according to which the volume changes are computed. But the blood-cells do not swell to so great a degree as is calculated, because their limiting membranes offer resistance. The blood-cell membranes are permeable to anions and impermeable to cations. The ammonium ion is an exception; in an ammonium chlorid solution the blood-corpuscles swell and are hemolyzed, because evidently the cation as well as the anion penetrates. The different anions penetrate with varying degrees of rapidity depending on the number of ions. Neither the tartrate nor the citrate ion penetrates the blood-cell. Anelectrolytes have no osmotic pressure effect on the blood-cells, which are hemolyzed in solutions of such substances. The volume of the blood-cell, which is dependent on the hydrogen-ion concentration of the external fluid, swells in an acid, and contracts in a basic fluid; this change in volume is caused by an increase of the number of osmotically active components inside the blood-cell as a result of the addition of acid.

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**Glucose Content of Human Erythrocytes and Their Behavior in Isotonic Solutions.**

*M. Bocnninger, Biochem. Ztschr., 128:482, Berlin, March 28, 1922.*

The constancy of human blood sugar has been widely disputed. Innumerable blood sugar examinations in the most diverse diseases are recorded but no one has found high values in anemic or low ones in plethoric individuals. From a series of fasting blood sugar estimations it may be concluded that it is therefore inexpedient to refer total blood sugar to the plasma volume, and a series of communicated plasma examinations justify this conclusion. New experiments are communi-

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cated regarding hemolysis and increase in volume of human blood-corpuscles in isotonic grape sugar solutions, showing specially that increased volume depends to a great extent on temperature. Experiments on human and animal blood showed that a higher temperature accelerates increase in volume of human blood-corpuscles and accelerates a decrease in the animal ones. A similar result to that yielded by the animal experiment was obtained in experiments on human blood-corpuscles with cane sugar and milk sugar, viz., distinct decrease accelerated by higher temperature. This phenomenon may be due to chemico-colloidal processes.

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**Further Studies of the Permeability of Human Erythrocytes.**

*Ernst Wiechmann, Pflüger's Arch. f. d. ges. Physiol.*, 194:435, Berlin, April 20, 1922.

The author has previously shown that calcium ions inhibit the permeability of erythrocytes to bromin ions and that erythrocytes suspended for 2 hours at ice-box temperature in solutions of sulpho-stains do not take up stains perceptibly. In continuation of these experiments it has been shown that erythrocytes charged with carbonic acid at various temperatures and for various periods did not take up perceptible amounts of sulpho-stains (cyanol, light green FS, setopalin, Ponceau 2 R). The permeability of the red cells for bromin ions was also inhibited by substances of the digitalis and strophanthin groups. But it was impossible to determine whether the action of digitalis and calcium was identical, or whether it was a question of sensitization to calcium, both of which views are advocated by Zondek or von Löwi for the conditions in the heart. Digifolin and strophanthin inhibit hemolysis by hypotonia, the former more than the latter, which may possibly prove of clinical importance. Erythrocytes which, as a result of washing with 0.95% salt solution show a decreased resistance to hypotonic salt solutions as compared with unwashed erythrocytes, exhibit increased resistance on the addition of digifolin or strophanthin. The staining experiments show in the first place that the sulphate anion and the anion of the sulphacid stains do not behave the same. The former, under the influence of carbonic acid, permeates the red cell, while the latter does not. In the second place they show that there is a true impermeability to stains, which is of importance in the theory of vital staining.

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**The Effect of Stimulating Substances on the Rapidity of Sedimentation of Red Blood Cells.**

*Hanns Löhr, Ztschr. f. d. ges. exper. Med.*, 27:1, Berlin, March 25, 1922.

Fahraeus and the Höber school regard phenomena of electrical charging of the red blood cells themselves as responsible for changes in the rapidity of their sedimentation, while Plaut and others seek an explanation in auto-agglutination, which they think is dependent on the fibrinogen content of the serum. According to Sachs varying rapidity



of sedimentation is due to variation in stability of the plasma, in which fibrinogen is the most changeable component. Sachs thinks the effect of protein body therapy is due to a change in the colloid stability of the body fluids. The author tested the effect of stimulating therapy on the rapidity of sedimentation of the erythrocytes. Blood was taken for a first examination of the rapidity of sedimentation and stimulating substances injected immediately through the same needle. Then blood was taken each hour for sedimentation. The tubes used were 6.5 cm. high and 5 mm. in diameter, graduated at 6, 12 and 18 mm.; 18 mm. proved not a very considerable sedimentation for a day. On intramuscular injection of 5 c.c. milk, 1 c.c. caseosan or 1 c.c. albumin preparation 304, a considerable quickening of sedimentation appeared within two to four hours and lasted for even a week. The same was true in intravenous administration of the substances, except that sedimentation appeared quicker, within the first hour. Colloidal silver preparations also act as stimulating substances. Pure silver, salvarsan, sodium chlorid, etc., may cause changes in dispersibility in the organism by catabolism of homologous albumin. As to these changes being caused by omnicellular processes, the author rejects the theory that it is a question of "shock" of the autonomic system. He saw quickening of sedimentation after adrenalin as well as after pilocarpin and thinks this is due to increase of the agglutination titer. In transfusion with the blood of a relative in pernicious anemia the rapid sedimentation was markedly inhibited by the transfusion of 0.5 liter defibrinated blood; but blood transfusion had no effect on the rapidity of sedimentation in a case of myeloid leukemia. Among 30 cases observed there were only two exceptions to the law that rapidity of sedimentation is hastened by the injection of stimulating substances.

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**Phagocytosis as an Expression of the Life of the Leukocyte.  
A Study of the Duration of Life of the Polynuclear Leukocyte.**

*J. de Haan, Pflüger's Arch., f. d. ges. Physiol., 194:449, Berlin, April 20, 1922.*

Phagocytosis is dependent on the relation between the surface tensions of the 3 bodies involved, namely the leukocytes, the surrounding fluid and the object to be phagocytized; the resultant of the physical forces is a force which drives the molecules into the protoplasm of the cell, so that unfavorable conditions of viscosity phagocytosis takes place. In accordance with this theory of Rhumbler, changes in phagocytosis may take place on account of different influences springing from the physical conditions and do not necessarily have anything to do with the phagocytic strength of the leukocytes. But in ameboid movement the varying condition of the cell protoplasm, which is continually under the influence of the metabolism of the cell, plays a great part. It has been found that a cell in a medium in which it formerly had phagocytic characteristics, when brought under the influence of various conditions no longer shows phagocytosis if in the meantime it has died. The cessation of phagocytosis under such conditions, as well as of ameboid movement, may be used as a criterion for the death of the white blood-cells.

Leukocytes were obtained from the exudation which was formed in the peritoneal cavity of rabbits and other animals after the injection of 200 c.c. salt solution. A comparison of different mediums showed that only undiluted homologous serum could be regarded as a physiologic medium in which leukocytes can be kept alive for a long time; other fluids, such as physiologic salt solution, Ringer's solution, ultrafiltrate of serum and even dilutions of serum, are just as poorly adapted for the purpose as other fluids which contain other colloids than the serum. While in general phagocytosis is a criterion of the life of the cell, there are exceptional conditions where this parallelism does not seem to exist, and dying or even dead leukocytes keep their phagocytic capacity almost unchanged. Such may be observed, for example in chloroform intoxication. The normal life of the polynuclear leukocyte in circulating blood is probably extraordinarily short. Although in the circulating blood in the large vessels they might remain alive longer, they are soon caught in capillary areas and destroyed, particularly in the spleen and bone-marrow. This process is essentially the same as that which takes place in an inflamed capillary region, i. e. mass emigration and destruction of leukocytes, a real physiologic inflammation.

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**The Toxicity of Acids for Leukocytes, as Indicated by the Tropin Reaction.**

*Alice C. Evans, J. Immunol., 7:271, May, 1922.*

The results of these experiments do not indicate definitely whether in cases of acidosis the leukocytes may be injured by the acid by-products of the infecting organism. Judging from what is known concerning variations in reaction of the body fluids during life, it appears that the leukocytes are protected by the buffer action of the blood against variations in pH which would be injurious. It must be borne in mind, however, that the acids produced by pathogenic bacteria are those which might have a specific toxicity for leukocytes. Moreover, the effect on the leukocytes is cumulative. It seems quite possible that leukocytes gathered at the site of an infection and continuously bathed in body fluids containing traces of the acid by-products of the infecting organism may suffer injury which would affect their capacity for phagocytosis.

It was found that leukocytes absorb H ions from weakly acid solutions, and if the quantity absorbed is great enough, the capacity of the leukocytes for phagocytosis is injured. In addition to the toxicity of the dissociated H ions, lactic, acetic and butyric acids have a specific toxicity for leukocytes. The order of the toxicity of the tested acids is: HCl and citric are less than lactic, which is less than acetic and butyric. When phagocytic tests are made in vitro it is necessary to protect the leukocytes against exposure to acid solutions. This is accomplished by the use of a buffered saline solution. It may appear that such a precaution is unnecessary if proper care is taken for the cleanliness of glassware. The tables given show that the leukocytes withstand one washing in an acid solution of pH 4.6 without any evidence of an inhibitive phagocytosis. But they also show the injurious effects of much weaker acid solutions when the exposures are repeated.

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Before the sensitiveness of leukocytes to acids was taken into consideration it happened rather frequently that the routine quantitative tropin test for the potency of commercial antimeningococcus serum failed. The present work perhaps will explain why this test has been unreliable. This is what may happen when all due care is taken for the cleanliness of glassware. The citrate solution used for taking up the pleural exudate may be of an acid reaction. The leukocytes are exposed to a comparatively large quantity of it. Then they are washed in a large quantity of saline solution. If it is unbuffered, and has been allowed to stand with no protection from the air of the laboratory other than the cotton plug, it may have absorbed enough  $\text{CO}_2$  from the atmosphere to bring the reaction to as low as pH 5.8. The leukocytes are again exposed to the saline solution in smaller quantity when it is added for making final suspension. Thus they may be subjected 3 times to the effects of acid solution.

The demonstration of the injurious effect of acid citrate on the phagocytic activity of the leukocytes, together with the finding of commercial sodium citrate preparations of an acid reaction, lead to the practical conclusion that when sodium citrate solution is used for preventing coagulation of body fluids containing living cells, it is a matter of importance to ascertain that the solution is not of an acid reaction. On the other hand the leukocytes were apparently unaffected by solutions of slightly alkaline pH values. A solution of the most alkaline citrate preparation encountered in these experiments (pH 8.8) did not harm the leukocytes perceptibly. The union of the immune body (bacteriotropin) with the streptococcus was not influenced by such variations of pH as were studied in these experiments.

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**The Reactions of the Oxydases of Human Leukocytes. Degeneration of Neutrophils Shown by the Aid of Indirect and Direct Oxydases.**

*Noel Fiessinger and Pierre Mathieu, J. de physiol. et de path. gén., 20:49, no. 1, Paris, 1922.*

The authors have examined the granulations in degenerated neutrophil and polynuclear leukocytes, obtained from blood, pus or exudates. The cells must be examined without spreading, fixation or staining, for comparison with the treated cells. The oxydases are examined by 2 processes. The first, that of the synthesis of idophenol blue, comprises fixation of the dried spread for two minutes in a mixture of 9 parts of 40% formalin with 1 part 95% alcohol. The slide is then treated with a mixture in equal parts of 2 solutions, both ten days old: alpha naphthol, 1 gm.; absolute alcohol, 30 gm.; concentrated ammonia, 2 drops; distilled water, 100 gm. The second solution is 1% paraphenylendiamin, in water. The second process omits fixation, the slide being treated with 75% alcohol, 100; benzidin crystals, 0.5; hydrogen peroxid, 0.2. The solution acts for fifteen to twenty minutes. The slide is then washed, and dried with absorbent paper. A methyl eosin stain is sometimes used with this process. Alpha and epsilon granules appear to be oxydasic. The reaction is peripheral, and best shown by the larger acid (eosinophilic) granules.

The degeneration of neutrophil leukocytes principally affects the nucleus and granules. The granules tend to merge, vacuoles are formed, fatty degeneration occurs and the oxydasic reactions cease. The process is more or less variable. The leukocytes often burst, projecting granules which retain their oxydasic reactions for a time. The eosinophils are especially resistant to the degenerative changes. The granules of leukocytes circulating in the blood may be affected by terminal trichinosis, typhoid at the fourth week, terminal influenzal pneumonia, or acute lobar pneumonia. Graham's granulation types, of 4 classes, were examined with reference to various chronic and acute affections. In grave diseases, and usually just before death, the oxydasic reactions appear to be altered. No other rule can be stated. The reactions indicate that the cells take up oxygen and liberate hydrogen. The granules of the leukocytes are complex protein, lipoid and probably metallic, compounds. The lipoid periphery elaborates a ferment which is oxydasic and which may escape from the cell by cytolysis. This ferment is absent in the undifferentiated cells of acute leukemia. It is therefore important in the functional differences of leukocytes.

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**Specific Determination of Migrating Mononuclear Cells in the Intestinal Epithelium and Study of Their Function.**

*Alfredo Corti, Haematologica, 3:121, Naples, March, 1922.*

Resuming the study (initiated in 1912) of some special free cells found in the stroma of intestinal villi in hibernating animals, Corti tends to interpret these cells as lymphocytic, and as having a catabolic function. They are characterized by containing an abundant number of blood-cells in various stages of disintegration, from normal to simple granular forms derived from such blood cells. Similar pictures of erythrophagia are also found in the spleen of these animals, especially those of long hibernation; therefore the author feels justified in assuming that we are here confronted with cellular elements whose special function it is to select, absorb and eliminate those erythrocytes which are no longer capable of discharging their proper function. As for the morphologic interpretation of these mononuclear cells lying free in the intestinal epithelium of mammals, all their characteristics tend to stamp them as belonging to the true lymphocytes. Some of them are said to exhibit vital manifestations which could be interpreted as phenomena of secretion; others may be regarded as discharging the function of elimination of erythrocytic materials.

This phagocytic property of the lymphocytes with respect to red blood-cells is not totally unconnected with the phenomenon of eosinophilia. In normal conditions the secretion of the leukocytes is poured, in liquid form, into the surrounding medium (the plasma); in conditions of loss or marked change in this medium the secretion crystallizes and assumes the form of visible cells. Hence the relation between eosinophilia and leukocytic activity in general, as well as with coagulation of the blood.

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**The Experimental Production of Macrophages in the Circulating Blood.**

*Miriam E. Simpson, J. Med. Research. 43:77, April-May, 1922.*

The study of macrophages is possible because they can be produced in the circulating blood by chronic intravenous injections of (1) colloidal dyes, such as Niagara blue 2 B; and lithium carmin; (2) larger colloids and suspensoids, such as red gold in sodium lysalbinat solution, India ink, and lamp black in gelatin solution; and (3) certain proteins or split products of proteins; gelatin; sodium lysalbinat. These 3 kinds of agents stimulating the production of the macrophages in the circulating blood, all contain some substance in the colloidal state, and this appears to be the only common factor. It seems probable that the effective action of the members of the second group depends upon the presence of the protective colloids. Attempts to determine a stimulating action peculiar to the higher colloids and the suspensoids were unsuccessful because of their instability in the absence of the protective colloids.

Macrophages are not found constantly in the blood of chronically injected animals but appear in showers; that is, the animal after a time responds to each injection by pouring great numbers of cells into the general circulation. The cells are distributed unevenly, few or none appearing in the peripheral blood, more in the venous blood of the heart, and the largest number in the venous blood from the hemopoietic organs, especially the liver and the spleen; the difference in the content of the two ventricles is very striking. The macrophages appear to be produced greatly in excess of the number needed to handle the foreign matter injected, and with their appearance marked changes in the platelet content and in the coagulability of the blood occur.

The monocytes and macrophages can be separated from the lymphocytes by means of a supravital stain of the living cells, but when present simultaneously in large numbers can not be distinguished by the oxydase, Giemsa, supravital, or other stains, though it may be possible to separate them by their ability to stain with the vital benzidin dyes. The two types of cells may at times act independently; but they have many of their biologic reactions in common.

The macrophages during the greater part of the treatment are uncommon in the main circulatory current; the monocyte group can, however, always be recognized, and while they may be increased in number (monocytosis) they retain their typical or normal morphology. During the macrophage showers the monocytes and macrophages are related not only by staining and by other tests but also by the presence of many intermediate cell types. A conversion of monocytes into macrophages if it does occur is limited and does not take place indiscriminately in the general circulation. While the available evidence indicates a close biologic relationship, the identity of these 2 types of cell has not been proved.

An excellent bibliography is appended.

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**The Leukocytic Inclusion Bodies of Barranikow-Döhle.**

*H. Accoyer, Presse méd., 30:401, Paris, May 10, 1922.*

Twelve years ago Barranikow, then Döhle, described, in patients with scarlet fever, some basophil granules, to the number of 1 to 3 per cell, in the polymorphonuclear neutrophils. They stained easily, especially by borax-blue. The author, in studying these peculiar corpuscles, examined the blood of subjects afflicted with different infectious diseases in different phases of their evolution, and also of healthy subjects. These inclusion bodies vary in volume and form. They may be round, oval, or triangular with rounded angles. They are often found at the periphery of the leukocyte. They stain a pale gray-blue. Some have a vague and indefinite contour, others are stained as intensely as the nucleus, and are attached to it by a thin band of nuclear substance; they are rounded or oval and constitute a small diverticulum of the nucleus; there may be 1, 2, or rarely 3 of them. These corpuscles are not characteristic of scarlatina and have no diagnostic value. They are observed in small number in healthy subjects. They are more frequent in diseased subjects, and especially when fever is present. Their number seems to correspond to the elevation of temperature.

In the production of these corpuscles the nucleus plays only a passive rôle; the active rôle is played by the cytoplasm. Their genesis is explained by a mechanical action of the protoplasm upon the nucleus. They are not made exclusively in the hematopoietic organs. The leukocytes of the nongranular series always preserve their normal aspect in cases where the percentage of neutrophils containing the bodies of Döhle increase. These formations have never been noted in the protoplasm of large mononuclears.

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**Laboratory Tabulator is Aid in Making Differential Blood Count.**

*C. Peñflor, Mod. Hosp., 18:551, June, 1922.*

Peñflor has devised a small tabulator which is of great aid in making a differential count of blood corpuscles. He claims that the apparatus facilitates differential blood counting; insures accurate and exact results; gives offhand the percentages of the white corpuscles after one counting without further figuring; avoids fatigue and weakening of the eye; can be used for making differential counting of pathologic erythrocytes, or for any other examination which involves percentage estimation. The instrument measures 6x6x1 $\frac{7}{8}$  in. and has a key-board similar to that of an ordinary typewriter, which can be operated with one hand, leaving the other free for focusing the relative position of the plate and microscope. In the operation of this machine all that is necessary to remember is the relative position of the keys corresponding to the different kinds of white corpuscles. The required key is depressed in succession as many times as the corresponding corpuscle appears in the field under observation in the microscope. The machine adds each variety of corpuscle as it is registered, and when

the total reaches 100 or a multiple thereof, up to and including 500, a bell rings. The operator can read the sums of individual counts, which will give the percentages direct if the total is 100.

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## 1f. PATHOLOGY.

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### An Instance of Supernumerary Stylohyoid Muscle.

*E. Olivier, Bull. et mém. Soc. anat. de Paris, 92:138, March, 1922.*

The extra muscle was observed during dissection. It was thin and flat, and inserted, above, by a tendon 1 cm. long, on the apex of the styloid process of the temporal bone, between the stylomaxillary ligament and the usual superficial stylohyoid muscle. The stylomaxillary ligament was adherent to it. The thin muscle tissue was contained in a sheath derived from the aponeurosis which extends from the angle of the jaw to form the floor of the submaxillary region. It was 6 cm. long and inserted on the tip of the little horn of the hyoid bone by a short tendon, 1 cm. in length, which surrounded the hyoid attachment. The supernumerary muscle was therefore deeply situated. It was necessary to separate the insertions of the normal, superficial stylohyoid muscle in order to reach the deep, new muscle, which replaced the stylohyoid ligament, of which no trace could be discovered.

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### Gynecomastia.

*Th. Tobler, Schweiz. med. Wchnschr., 52:412, Basel, April 27, 1922.*

The patient was a male 44 years of age. He led a peculiar life, had a male voice, never had prostatitis or orchitis and came to the hospital with signs of cardiac decompensation. He died shortly after admission. Autopsy showed mitral insufficiency, cardiac hypertrophy, signs of passive congestion, bilateral gynecomastia of moderate degree, bilateral atrophy of the testicles, diffuse colloidal struma and a slight chronic internal hydrocephalus. Histologic examination of the glands of internal secretion showed diffuse colloid struma of the thyroid. The pineal gland and its 2 septa showed on histologic examination the changes found in the senile. Eosinophile cells predominated in the pituitary body, there were few basophile cells and the principal cells were irregularly distributed in the entire anterior lobe. The pancreas was normal. The mammas were enlarged, the connective tissue increased, there were many gland ducts but they did not form gland lobules. The testicles were atrophic, the epithelium of the tubules consisted almost exclusively of undifferentiated spermatogenous cells, and the few interstitial cells were apparently in a stage of degeneration.

Gynecomastia may result from under developed testicles which have degenerated and undergone the same pathologic changes as occur after castration. Such changes may be absent and the gynecomastia may be due to effects of the other endocrine glands or malformations of them. Enlargement of the breasts is usually due to fat and connective tissue

increase, more rarely to increase of gland tissue. Genuine gland lobules with terminal bulbs were never found. The fluid expressed from the breasts of gynecomasts contains mucus and epithelium in a stage of fatty degeneration. Only the hormone of the corpus luteum can produce secretion of milk and all reports of secretion of milk in the cases of gynecomastia are fabulous.

This case corresponds to the gynecomastia of a late castration.

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**Occurrence of Hair on Supernumerary Nipples.**

*Yrjö Kajava, Anat. Anz., 55: 323, Jena, April, 30, 1922*

While hair does not occur on normal nipples, except embryonal ones, it is frequently found on supernumerary mammary glands either in the center or at the margin of the nipple-cone. About 12% of all cases of hyperthelia possess hair. Microscopical examination shows that the hairs are generally not developed very strongly and the hair-follicles are always connected with sebaceous glands. Together with well-developed sebaceous glands solid epithelial columns occur that are to be regarded as undeveloped hair rudiments, the same as those observed in the embryo by Eggeling. The hairs are 2 or 3 in number and usually run parallel to, but not in, the longitudinal mammillary axis. Thus, the hair rudiments, which disappear in the case of normal mamillas persist in the rudimentary supernumerary structure, so that equilibrium may possibly exist between the mammary gland rudiment on the one hand and the hair rudiment on the other in the sense that the hair rudiments are developed more strongly the more rudimentary the mammary gland rudiments. An analogous relation exists between a hair and the sebaceous gland connected with the hair-follicle.

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**A Case of Congenital Narrowness of the Trachea and Bronchi, Absence of the Membranous Wall of the Trachea, Formation of Diverticulum, etc.,**

*Alfons M. Sankott, Wien. klin. Wchnschr., 35: 391, April 27, 1922.*

In a man of 36 who died of nephritis, the trachea and bronchi were abnormally small. The trachea had segments of varying diameter, the smallest being 12 mm. smaller than normal. Moreover the trachea did not have any membranous wall except for a short distance. This was explained by the fact that the cartilaginous rings were completely closed except at one small place where the membranous wall existed. Some of the cartilaginous rings were spread, forked and connected by bridge-like processes. The first 2 open tracheal rings ended abnormally in a tip which was bent out of the horizontal in a caudal direction, to end near the median plane in the membranous wall. Moreover a solitary cartilaginous plate was embedded in the membranous wall, below which there was a diverticulum 11 mm. long. The right bronchus was 6 mm. smaller in diameter than normal, the left bronchus 4 mm. The structure of the bronchial wall was normal. The same was true of the branches of the bronchi. The dorsal and ventral branches, with

the exception of the first dorsal, originated on the right side, as in the normal bronchial tree which sprang from the first ventral bronchus. This was doubtless a case of congenital malformation of the trachea and bronchi.

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**A Study of Heart Malformations Based on a Case of Congenital Defect in the Membranous Ventricular Septum and a Defect in the Apex of the Tricuspid Valve Adjacent to this Septum Defect.**

*Kurt Gutzeit, Virchow's Arch. f. path. Anat., etc., 237: 355, Berlin, March 28, 1922.*

In the autopsy of a 26 year old woman who died after delivery, there was a defect in the membranaceous septum of the ventricle with embryonic puffiness and thickening as well as dwarfing of the tricuspid valve adjacent to this defect, and a fissure in the valve segment, as well as hypertrophy and dilatation of the right heart and weakness of the left ventricle.

Probably every septum anlage has an excess of vital energy over that required for its development until it unites with the opposite side, this surplus of energy being very variable, so that one side may have a more rapid and extensive growth and the other a slower growth; this results in a union of the two halves sometimes to one side, sometimes to the other, of the midline, according to whether one side or the other grows more rapidly. Naturally the surplus of energy is obliterated at the moment when the two halves unite. Union would take place even if the surplus of vital energy of the septum anlage were lacking. But if the tendency to growth in one side of the septum passes beyond the physiologic point in a negative direction, a defect occurs unless the surplus of energy of the other side is sufficient to fill it in. If there is such an inhibition of growth on both sides, the defect is larger and extends farther toward the side whose vital energy is the least.

As to the defect in the septum in the above case, primary and secondary endocarditis could be definitely excluded. The sharp and delicate edge of the defect, the lack of an indentation toward the right, the lack of any signs of an old endocarditis in the whole valvular structure and the thickened middle tip of the tricuspid led to the conclusion that the case was one of pure inhibition of development. With reference to the defect in the middle septum of the tricuspid valve, histologic examination showed no signs of an inflammation, but showed areas stained red and rich in nuclei, which were probably embryonic muscle cells.

This case supports the theory that valve anomalies are a true inhibition of development and do not originate from inflammation, not even from a secondary endocarditis resulting from a primary inhibition of development. The whole malformation can be explained from the point of view of developmental history by assuming that from some unknown cause the right end of the fused lips of the endocardium, particularly its posterior part, had suffered a loss of vital energy, so that the membranous part as well as the middle tip of the tricuspid could not finish its physiologic development. To explain the dilatation

of the pulmonary artery, it must be assumed that this dilatation was due to the abnormal distribution of blood in the heart chambers and the more than normal demands made on the artery. The pulmonary artery, which on account of the increased pressure in the hypertrophied right ventricle, received more blood than normal, and whose internal pressure was increased in the same proportion as that of the right ventricle, dilated, adapting itself to the changed pressure conditions in order to allow the larger amount of blood to pass more quickly, and thereby to decrease the internal pressure.

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**Three Chambered Heart with Atresia of the Left Venous Opening.**

*Max Dudzus, Virchow's Arch. f. path. Anat., etc., 237: 32, Berlin, March 18, 1922.*

In a girl four weeks old there was atresia of the left venous ostium, complete absence of the ventricular septum, corrected transposition of the great vessels, and two openings of the margin of the septum of the foramen ovale, with closed Botalli's duct. The cause of this malformation of the heart is unknown; it originates in the fourth week of embryonic life. The defect in the auricular septum is the result of atresia of the left venous ostium.

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**Persistent Cardinal Veins and Absence of the Inferior Vena Cava.**

*V. Košir, Anat. Anz., 55: 365, Jena, May 20, 1922.*

In the abdominal cavity of a child about 6 months old there was on the left side of the aorta a large vein into which the two common iliac veins emptied. This vein passed through the diaphragm with the aorta, passed back of the aorta to the right side of the body and in its further course followed that of the azygos vein. Into this vein emptied the veins of the kidney and suprarenals and of the body wall; the latter were also connected with each other by longitudinal anastomoses. This "large body vein" was made up of the caudal part of the left and the cranial part of the right posterior cardinal vein and bore no relation to an inferior vena cava. The hepatic veins emptied independently into the right auricle.

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**Supernumerary Hepatic Lobes. A Unique Case of a Supernumerary Lobe Implanted on the Gall-Bladder.**

*Frédéric Corsy, Marseille-méd., 59: 442, May 1, 1922.*

This supernumerary lobe measured 17 by 10 by 4 mm. It was implanted on the gall-bladder by means of a short mesentery. Another portion of the gall-bladder was also connected with the quadrate lobe by a bridge of liver tissue. This anomaly is explained by supposing that the gall-bladder was primarily completely buried in the liver, the

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overlying portion of which mostly atrophied later, leaving behind only the aberrant lobule and the abnormal connection with the quadrate lobe. The author classes supernumerary lobes of the liver into 2 groups: (a) Anomalies through excess of an atrophic process, resulting in the formation of a membranous bridge uniting the 2 portions of a lobe. (b) Anomalies through arrest of this process. The liver is then normal in all its parts, but on its surface is found a more or less pediculate supernumerary lobe. A number of cases found in the literature are classed by Corsy according to this conception.

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**A Third Testicle as an Appendage to the Intestine.**

*A. J. F. Oudendal, Virchow's Arch. f. path. Anat., etc., 238:82, Berlin, April 22, 1922.*

At the necropsy of a Hindoo, about 30 cm. above the ileocecal valve, there was a cord 4.5 cm. long on the end of which hung a body the size of a dove's egg, which on cross section looked like a testicle. In the scrotum there were two normal testicles with marked spermatogenesis. This third testicle on microscopic examination showed a well-developed system of tubules with interstitial tissue tolerably rich in nuclei. The tubular epithelium was undifferentiated and corresponded to an early developmental stage of the testicle; it was impossible to decide whether it was a case of retrogression or of defective differentiation. Leydig's interstitial cells were present in very small numbers. The cord had no demonstrable lumen and only served to conduct nutritive blood-vessels and lymph-vessels.

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**Two Cases of True Hermaphroditism.**

*Walter Kolmer and Ferd Schminzky, Pflüger's Arch. f. d. ges. Physiol., 194:362, Berlin, April 20, 1922.*

In *Esox lucius* and *Salamandra maculosa*, species in which true hermaphroditism has not heretofore been described, ovum cells could be demonstrated in the testicle; in *esox* they were from 50 to 250 microns in size, and were present symmetrically on both sides of the body; in *salamandra* also they presented the picture of normal ovum cells. In ants this phenomenon is relatively frequent. The cells are markedly different in the arrangement of their chromatin from the spermatocytes and are to be regarded as true ovum cells. Possibly they play a part in the transformation described by Champy of female individuals into male ones under the influence of defective nutrition, or they may have been hermaphrodite individuals from the beginning.

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**Brachydactyly, Ectrodactyly and Syndactyly of the Left Hand and Both Feet.**

*E. François-Dainville and R. Léonard, Bull. et mém. Soc. anat. de Paris, 92:106, March, 1922.*

The right hand was normal. In the left hand, the phalanges were  
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subluxated outward and forward on the metacarpals. The fingers formed merely an irregular fringe, or outline. The same conditions were present in both feet, the left being the more affected. The palate was vaulted asymmetrically and the teeth were irregular. Drawings are given. The patient, a man of 50, died of enteritis. Postmortem dissection was made. No hereditary character could be made out, nor could syphilis, alcoholism or consanguinity be determined. The extensor of the first finger reaches the back of the carpus beside the common extensor, crosses obliquely above the radial tendons and is inserted on the head of the first metacarpal.

The extensor of the second finger rapidly leaves the common extensor, passing obliquely to the first phalanx of the second finger. A third tendon parallels the preceding, terminating on the head of the second metacarpal. The extensor of the third finger is attached to the preceding for a part of its course, ending at the base of the first phalanx of the third finger and the articular capsule. The tendon of the fourth finger ends similarly.. That of the fifth finger ends on the head of the fifth metacarpal, constituting one of the divisions of the common extensor, which bifurcates. The interossei are atrophied and the superficial muscles abnormal. The superficial cannot well be distinguished from the deep flexor tendons. The vessels are normal well into the carpus. There is no palmar arch. Corresponding alterations occur in the feet. The condition is probably due to arrested development. The nervous centers could not be examined, but were probably atrophic.

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### **The Place of Pathology in the Practice of Medicine.**

*Walter V. Brem, California State J. M., 20:200, June, 1922.*

One of the difficulties of a laboratory is that frequently too much is expected of it, the limitations of various examinations being not fully understood. Very few laboratory tests are pathognomonic. Laboratory results should be considered only as evidence, to be weighed with all the other evidence, which the attending physician alone possesses. Cellular pathology is the most difficult of all laboratory examinations. Even the best trained pathologist is forced to say not infrequently that he is unable to venture an opinion regarding the malignancy of a specimen. Research, far better than anything else, will preserve and foster a scientific spirit in a laboratory. The writer's laboratory has been interested since 1912 in the treatment of syphilis, especially neurosyphilis, with the arsenicals. This investigation covering a period of 10 years not only has contributed a large and unusual series of cases carefully controlled by blood and spinal fluid tests, but has also aided materially in developing these tests to furnish special information that the clinician needs. Another investigation conducted by this laboratory for 10 years is that of blood transfusions, controlled by blood grouping as worked out by Moss. At first defibrinated blood was used, then citrated blood, and since 1916 whole blood by the Lindemann syringe method. The series of transfusions now numbers about 2000, and has taught valuable lessons which will soon be embodied in a report.

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**The Great Value of Autopsies.**

*B. T. Terry, J. Tennessee State M. A., 15:39, May, 1922.*

Terry stresses the fact that when a patient dies an autopsy is an excellent opportunity to supplement the clinical data already obtained with exact anatomical facts. The author submits in the article several case histories which it was possible to check up by necropsy, and in which the autopsy did one of three things: (a) Confirmed the clinical diagnosis, but added features which were not diagnosticated with certainty; (b) revealed very important lesions not suspected clinically, in addition to confirming the clinical diagnosis, or (c) made the diagnosis when during life exact diagnosis was impossible. In attempting to secure an autopsy it is important that a tactful approach be made to the head of the family of the deceased representing the possible advantages of the procedure to others, including the remaining members of the family. Terry believes the most satisfactory plan is to send the body to a pathological laboratory where the autopsy can be performed in detail, the necessary photographs taken, and the autopsy protocol dictated and recorded accurately in full as the autopsy proceeds.

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**Technic of Autopsies on the Auriculoventricular Bundle. Some Anatomic Findings.**

*O. Josué, Bull. Acad. de méd., 87:564, May 23, 1922.*

After opening the heart in the usual manner a search should be made for the portion of the interventricular septum which is particularly thin and transparent. This is located immediately below the angle formed by the posterior and the right semilunar aortic valves. On the right side, this membranous septum corresponds to the lowest portion of the right auricle and to the superior portion of the right ventricle. The upper part therefore separates the left ventricle from the right auricle and the inferior portion separates the two ventricles. This membrane is formed by fibrous tissue covered on both sides by endocardium and contains no myocardial tissue other than the auriculoventricular bundle. It is connected behind with the fibrous auricular partition. Tawara's node and the beginning of the bundle are located on the right surface of this partition. The bundle then penetrates into the membranous septum, being found sometimes near its inferior border but always separated from the myocardium by fibrous tissue. It divides into right and left branches during its course in the septum.

This membranous region should be inspected carefully on both sides, and by transparency in order to detect macroscopic lesions, such as gummas, atheromatous patches, ulcers. For histologic examination a block of tissue including this region should be cut by the technic of Monrad-Krohn. In some cases the bundle penetrates into the fibrous tissue in an irregular manner, which might be wrongly interpreted as a dislocation of the bundle by sclerosis. It may be either triangular, round or ellipsoid. In one case the author found it separated into two fragments by a band of fibrous tissue.

The structure of the left branch differs from that of the trunk  
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and is more like the rest of the myocardium. The cylindric fibers, however, are thinner. They are less clearly striated and have more nuclei. Finally they do not stain quite so well with picric acid as ordinary myocardium.

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**Simple Apparatus for Cutting Frozen Sections with Minot Microtome.**

*Chauvin and Vigne, Marseille-méd., 59: 439, May 1, 1922.*

The apparatus devised by the authors has more or less the same shape as the specimen holder of Minot's microtome, but has a hollow part on which the table is screwed as a cover. The apparatus is filled with carbon dioxid snow, and the specimen placed in a drop of water on the striated surface of the table. Freezing takes place within two minutes and a temperature of  $-12$  to  $-20^{\circ}$  C. is obtained for about twenty minutes. This apparatus is economical and with it successive phases of freezing and melting, which are very harmful to the tissues, are avoided. The use of water for the preparation of frozen sections has certain disadvantages, for ice is made up of fine needles which have a destructive action on the tissues. The authors recommend the following improved technic: As soon as the specimen is cut, it is placed in ordinary sugar syrup. Half an hour later it is transferred to gum mucilage, and the specimen is frozen on the microtome table in a drop of this gum mucilage. The resulting mass is yellow-white and firm without being hard. This gives very good frozen sections measuring about 12 mm. by 10, and 0.125 mm. thick.

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**The Theory and Practice of Preserving Specimens in Their Natural Color.**

*Carl Kaiserling, Virchow's Arch. f. path. Anat., etc., 237: 467, Berlin, March 28, 1922.*

Among the different methods of preserving anatomic specimens in their natural colors for museum purposes, only those of the author and Jores have proved generally effective. Kaiserling reports supplementary studies of the theoretical principles of his method. He first tested the action of pure formalin on a solution of blood pigment. A 2% solution was used with a pronounced oxyhemoglobin spectrum (bands: 589-573, 556-530, end absorption from 470), and pure formalin was added drop by drop. As Benedecenti has previously shown, the stripes become paler and narrower, the solution turbid, and after an hour stripes can no longer be seen. The spectrum of formalin blood seems to be that of methemoglobin. If alcohol is added to this blood there is a floccular bright red precipitate, fixed clots or organs become bright red in a few minutes and give a two-banded absorption in the spectrum of 575-555 and 545-520 and end absorption at 500. If the alcohol is allowed to act for 24 hours there is a weak absorption before the first stripe at 585, and in thicker layers at 590, and a shadow between the chief stripes. This spectrum corresponds to the cathemoglobin of Klaveren. The addition of salts causes a delay in the hardening of

the organs. The preservative fluid of glycerin, potassium or sodium acetate and water does not change the cathemoglobin color, and preserves it.

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**Findings in the Hypophysis in Acute Infectious Diseases.**

*Alfred Plaut, Virchow's Arch. f. path. Anat., etc., 237: 165, Berlin, March 18, 1922.*

Of 35 cases of sepsis, metastatic disease of the hypophysis was found in 18, most frequently in endocarditis and staphylococemia. Microscopic examination of the hypophysis in a number of cases of infectious disease, but not septic in the ordinary sense of the word (pneumonia, typhoid, scarlet fever, measles and whooping-cough) did not show any positive results. In 26 necropsies in cases of grip (12 in the period from December, 1918 to February, 1919, and 14 from the epidemic of 1919-20), hemorrhage was found in the anterior lobe of the hypophysis in only 1 case — that of a woman of 30 years. All of the patients with 1 exception died of lung complications; 4 had empyema. In 1 case of typhus, swollen endothelial cells had been discharged into the lumen of many of the capillaries of the neurohypophysis; they resembled plasma cells. This was not observed in a second case.

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**A Case of Isolated Amyloidosis of the Heart.**

*Gustav Kann, Virchow's Arch. f. path. Anat., etc., 237: 22, Berlin, March 18, 1922.*

The changes were found in the cadaver of a 77 year old man who had died of carcinoma of the esophagus. Macroscopically the heart did not show the signs characteristic of amyloid, but microscopically all parts of it were found heavily infiltrated with amyloid. It was noteworthy that the conducting system was found involved to as severe a degree as the other parts of the heart. According to the histologic picture where the greater part of the muscle elements were seen to have undergone atrophy or even entire destruction from the pressure of the surrounding amyloid masses, there must undoubtedly have been severe functional disturbances of the heart, at least toward the end of life. Unfortunately no clinical observations had been made which would contribute to a clearing up of the nature of the heart disturbances caused by such a condition.

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**Histology of the Tuberculous Primary Focus in the Lung.**

*Alexander Kebben, Virchow's Arch. f. path. Anat., etc., 237: 224, Berlin, March 18, 1922.*

In 7 patients from 5 months to 4½ years of age the author made histological examinations of the primary focus in the lung. He found that in the beginning this was always a caseous pneumonia, with a wall of tuberculous granulations around it. In only 2 cases did the primary focus stop at this stage of development. In the other cases a pre-



dominantly granulating tuberculous disease of some bronchioles and alveoli developed, and it was found that these bronchioles had some sort of connection with the primary focus. Either they branched off from the chief bronchus which passed through the focus, or they passed so close to the focus or even through the edge of it, that the caseous material ruptured into the lumen at some point. The histological findings therefore indicate aërogenic infection. It is probable that the bacilli first settle in the wall of a bronchus 1 to 2 mm. in diameter, and from this point the caseous pneumonia develops that forms the center of the focus, leading later to the above described changes.

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**The Regenerative Processes in Tuberculous Ulceration of the Intestine.**

*H. Schünemann, Virchow's Arch. f. path. Anat., etc. 238:135, Berlin, Apr. 22, 1922.*

It is known that the intestinal mucosa has a capacity for regeneration after defects, and tuberculosis, typhoid and dysenteric ulcers are covered from the edge with new-formed epithelium, which consists at first of pavement cells which pass gradually into the adjacent cylindric epithelium. But as the character of intestinal tuberculosis is progressive, complete regeneration is rare, and cicatricial healing is more frequent. Almost always there are places at the base of tuberculous ulcers that are covered with new epithelium, the origin of which was studied in serial sections. These showed first that as soon as there is a disturbance of tissue by the tuberculous process, proliferation of the adjacent gland epithelium begins at once. The new-formed gland tubules may penetrate so far into the deep tissue that their deepest parts, under favorable conditions, are spared by the destructive process; they are often found even between fibrils of the muscularis that have been pushed apart, and after cleaning of the ulcer they may become the starting point of regenerative proliferation of epithelium. The implantation of free overhanging ulcer edges, as suggested by Amenomya, should therefore be rejected. In tuberculous processes there are no such cystic structures as are brought about in the healing of dysenteric ulcers by increased secretion; only here and there are small cysts on the edges of the ulcers, caused by the occlusion of a gland tubule.

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**Pathologic Changes in Mixed Infection with Dysentery and Enteritis (Paratyphoid or Gärtner) Bacilli.**

*César Bordoni Posse, Virchow's Arch. f. path. Anat., etc., 237: 380, Berlin, March 28, 1922.*

Dysenteric changes in the intestine, found in cases of paratyphoid, have often been attributed to the action of the paratyphoid bacillus, but several investigators have shown that in such cases there is evidently a mixed infection with paratyphoid and dysentery bacilli. Pathologic changes characteristic of paratyphoid may be found in the intestine at the same time as those of dysentery. In the lower ileum, for example, typhoid-like ulcers, in the large intestine dysenteric changes, or the

paratyphoid changes may lie outside the intestine. If a mixed infection is demonstrated by pathologic and bacteriologic examination, it is often difficult to determine whether there was a true mixed infection, i. e. whether infection with both diseases occurred at the same time, or whether one infection was secondary to the other. One case reported shows that where there is a combination of the characteristic changes in the intestine caused by the enteritis bacteria and by dysentery bacilli, each of these changes may be definitely demonstrated bacteriologically. Other cases show that a combination of paratyphoid gastro-enteritis with dysentery can be demonstrated by pathologic examination. In the author's case there was, on the one hand, a Shiga-Kruse dysentery with sloughing and ulcer formation in the large intestine, and fresh sloughing in the lower small intestine, and on the other hand excessive swelling of Peyer's plaques and solitary nodules in the lower small intestine. Bacteriologic examination showed pure cultures of *Bacillus enteritidis* Gärtner in the bile and spleen and in the sloughs in the large intestine *Bacillus dysenteriae* Shiga-Kruse and *Bacillus enteritidis* Gärtner. Nothing definite can be said as to the time relation of the two infections. The conclusions are: (1) There has thus far been no proof that paratyphoid bacilli, particularly enteritis bacilli, can cause the characteristic picture of dysentery, sloughing and ulceration. (2) If the dysentery extends into the lower small intestine, the lymph structures, solitary nodules and Peyer's patches, are often involved in the sloughing inflammatory process. (3) Dysentery bacilli and enteritis bacilli may cause their characteristic pathologic pictures at the same time and can be demonstrated bacteriologically in these lesions at the same time. With dysentery changes in the intestine, there may be a paratyphoid pyemia with localizations (abscess formation) outside the intestine, or there may be in the intestine itself both the changes caused by dysentery bacilli and those caused by enteritis bacilli. The proof of a combined infection lies in the bacteriologic demonstration of Shiga-Kruse bacilli and Gärtner's bacilli. (4) The time relation of the 2 infections may vary and must be determined by clinical, anatomic and bacteriologicoserologic examination.

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**Pathogenesis of Cholera. V. "Intestinal Cholera" of Young Animals.**

*G. Sanarelli, Ann. d'igiene, 32:117, Rome, Feb., 1922.*

Notwithstanding the many new facts brought to light by this series of investigations on the methods of action of the cholera vibrio within the animal organism, Sanarelli maintains that the pathologic process in man is still far from being completely elucidated in its most characteristic and most important aspects, either from a clinical or an epidemiologic standpoint.

From experiments performed on suckling rabbits and guinea-pigs, he concludes: The stomach contents of young rabbits do not transport through the pylorus species of nonspore-bearing microorganisms. The very first bacteria lodging within the intestinal tract of new-born rabbits are anaërobes, which make their appearance in the large intestine

twenty-four hours after birth. The small intestine becomes invaded by bacteria many days afterward; the flora here is always scant, and uniformly more abundant in the lower than in the upper portions. The duodenum remains constantly sterile. The cholera vibrio administered orally to nursing rabbits produces a fatal pathologic process in the intestinal tract, which, however, has little analogy to true human cholera and could strictly be characterized only as intestinal or experimental cholera. Such a process could be induced without the aid of secondary microorganisms. However, there is a progressive increase in the natural resistance of young rabbits, so that, at about the tenth day of life, resistance to intestinal infection may be regarded as completely assured.

Cholera bacilli introduced into the oral cavity of nursing rabbits disappear from the buccal mucosa rapidly and progressively. This disappearance, at times surprisingly rapid, is no doubt facilitated by the bactericidal action of the mother's milk. In young rabbits dying of "cholera," even when the disease has been transmitted parenterally, there is constantly found an abundant outpouring of bacteria through the buccopharyngeal mucosa. Contrary to what has been observed in adult and in new-born guinea-pigs, gastric acidity of new-born rabbits, which is normally high, increases markedly as the intestinal disease process develops. The gastric juice, both of new-born and of adult rabbits, exerts an almost instantaneous bactericidal action on the cholera bacillus, as for that matter on all nonspore-bearing bacteria. Hence an injection of the cholera vibrio made directly into the stomach of a new-born rabbit, through the stomach wall, is perfectly harmless. This marked bactericidal property is due not alone to the presence of lactic and hydrochloric acids, but also to other thermostabile substances which, with respect to their solubility in chloroform and ether, behave strikingly like fatty acids and neutral fats. In this "cholera" of young rabbits, the organs showing a selective pathologic process and abundance of specific bacteria are the cecum, appendix and colon. The small intestine is usually very scantily invaded, when not totally sterile. The duodenum is invariably sterile. Therefore, not only bacteriologically, but also from a pathologic-anatomic point of view, this process cannot be regarded as a true cholera, but rather as a choleriform enterocolitis. Cholera bacilli introduced into the oral cavity do not reach the selective portions of the intestinal wall (through which they are excreted) directly by way of the stomach, but indirectly through the general circulation. In young rabbits a choleriform enterocolitis may equally be induced by inoculations of cholera bacilli under the skin, into the peritoneum or intravenously.

The bacilli administered orally to young rabbits are first absorbed by the lymphatic vessels, whence they reach the general lymphatic stream and the blood. They make their first appearance in the digestive tract after about twelve hours, and select for this purpose the ileum, cecum, appendix and colon. Later they also appear, in small numbers, in the small intestine, but never reach the duodenum. The first disease symptoms appear after twenty-four hours, and involve particularly the cecum and colon. Notwithstanding the disease, the infected rabbits continue to increase in weight until the day immediately preceding death. The advent of other bacteria, such as the colon bacillus, aggravates the intestinal affection, and makes it manifest even at a time when

the rabbit has reached a maturity which would ordinarily render him refractory to choleriform enterocolitis. Intestinal resistance begins to be manifest only about the tenth day of life, and thus coincides with the first appearance in the blood plasma of bactericidal substances (alexins). Failures attending all attempts at active vaccination or serotherapy for "cholera" in such new-born animals is due to absence of alexins. The appearance of specific antibodies within the blood may be induced only by vaccination of the mother animal, effected during the latter's pregnancy. Rabbits born of mothers so vaccinated are refractory also to choleriform enterocolitis. Cholera bacilli administered by mouth may eventually reach—in very limited numbers—the mucosa of the terminal portions of the intestinal tract, and are then expelled with the intestinal contents. The resistance exhibited by adult rabbits to vibrionic enterocolitis is due principally to a lessened permeability for the microorganisms on the part of the buccal mucosa as well as to a lower sensitiveness of the intestinal mucosa through which the bacteria are expelled.

Guinea-pigs, being born after a period of gestation of 60 days, are provided with a digestive system of much more complete development than rabbits, which are born after a period of only 30 days. Hence, not only is the permeability of guinea-pigs' buccopharyngeal mucosa more limited, but also the resistance of their intestinal excretory mucosa is more pronounced than in new-born rabbits. The acidity of the gastric juice in new-born guinea-pigs does not allow for the survival of cholera bacilli, nor of other nonspore-bearing bacteria administered by mouth; so that by the time these microorganisms reach the pylorus they are all dead. However, the bacterial proteins contained in these dead germs may, after passing out of the stomach, be absorbed by the intestinal mucosa and thus, after reëxcretion from the circulation, cause a gastro-enteritis due to elimination of toxins through these organs. Cholera bacilli administered by mouth to new-born guinea-pigs may—to a very limited extent—be absorbed through the lymphatics of the mouth, and later be eliminated, as usual, in the lower portions of the intestinal tract.

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**Chemical Studies on Intestinal Intoxication. I. The Presence and Significance of Histamin in an Obstructed Bowel.**

*R. W. Gerard, J. Biol. Chem., 52:111, May, 1922.*

The histamin present in fluid accumulated in closed washed loops of the jejunum of the dog was determined chemically by the author. Briefly, the method consists of acid hydrolysis of the protein material, distillation of ammonia, precipitation of the amins and amino-acids with acid phosphotungstic acid, decomposition of this precipitate with baryta, concentration, addition of NaOH to the concentrate, and repeated extraction of the alkaline solution with amyl alcohol to separate the histamin from histidin. The histamin is tested for, colorimetrically, by coupling with diazo-benzene sulphonic acid. As little as 0.001 mg. histamin dihydrochlorid (in 8 c.c. of test mixture) may be determined quantitatively in this manner. The tabulated results show the presence of histamin in 7 out of 8 loop fluids analyzed. This substance is present in the contents of isolated closed loops of the large or small intestine in

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amounts varying from 2-3 mg. histamin dihydrochlorid per 100 c.c. fluid. The fluid which contained no histamin had been formed under sterile conditions and had caused no symptoms. The presence of histamin in sterile as well as loop mucosa, however, forbids the conclusion that this amin can be formed only through the agency of bacteria. Gerard was able to show the presence of a peptamin histamin for 2 samples of loop fluid. The chemical properties and biologic action of closed-loop fluids may be accounted for by their content of free and combined histamin, though other toxins are surely present.

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**The Intestinal Form of Lymphogranulomatosis.**

*K. Terplan, Virchow's Arch. f. path. Anat., etc., 237: 241, Berlin, March 18, 1922.*

The author's case was in a woman 56 years old. Necropsy showed an extensive lymphogranulomatous gastritis and enterocolitis with perforation of two ulcers in the ileum. Macroscopically a diagnosis of tuberculosis was first made, but on more careful observation lymphogranuloma was suggested, which histological examination confirmed. The author collects the cases from the literature with a view to determining the etiology of this disease, which is not yet settled, nor is there any general agreement as to the portal of entry of the causative agent. From this point of view the cases of intestinal granulomatosis seem significant, presumably indicating that the digestive tract is the portal of entry. In every case search should be made in the affected lymph nodes, particularly in the respiratory and digestive tracts, for any granulomatous changes that could be interpreted as a primary focus.

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**An Unusual Finding in the Kidney.**

*Cornelia de Lange, Virchow's Arch. f. path. Anat., etc., 237: 276, Berlin, March 18, 1922.*

At the necropsy of a child 6 weeks old who had died of gastroenteritis, large cells were found in the convoluted tubules which at first sight looked like protozoa. It was a peculiar form of degeneration called frothy degeneration. But the nature and etiology of the change is unexplained.

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**A Study of the Reticulate Fibers with Special Reference to the Kidney.**

*Carl Krauspe, Virchow's Arch. f. path. Anat., etc., 237: 475, Berlin, March 28, 1922.*

Krauspe examined the reticulate fibers in over 500 organs, especially the kidneys. In the liver the fibers are a sort of supporting tissue whose relation to the individual tissue components of the different organs varies with their anatomic structure and functional needs. Therefore in organs depending on their structure, fibers are found which accompany



chiefly the vessels or the parenchyma, or both parts may be equally well developed. Certain organs can be grouped together with reference to their reticulate fiber framework, in which multicellular gland tubes are surrounded by a scarcely visible supporting substance. This includes organs such as the kidney, pancreas, salivary glands and mammary glands.

Krauspe examined 150 kidneys and in the glomeruli could demonstrate only a few delicate fibers. In the convoluted tubules, he found the same picture as Russakoff and Rühle. Toward the papillas the true reticulate fiber system became continually coarser; numerous collagenous fibrils and smooth muscle fibres mixed with it made the examination more difficult. On the whole they were circular fibrous membranes. No relation could be demonstrated between collagenous tissue and reticulate fibers in adults. Two systems could be distinguished, one accompanying the vessels and the other the tubules. From a study of the kidneys of three fetuses it seems that the reticulate fibers begin in a granular impregnation of certain cell borders and processes.

From an examination of certain pathologic conditions, including cortical cysts, cortical adenomas, fatty, amyloid hyaline degeneration, circulatory disturbances, tuberculosis and tumors, the conclusions are that the reticulate fibers are made up of the netlike tissue of Kölliker and the adenoid substance of His. Chemical examinations of the fibrous membrane have been made by Siegfried, who has found a specific substance, reticulin, in it; this was confirmed for the kidneys by Rühle. Almost all investigators believe that the reticulate fibers originate from cells. Capillary endothelial cells and undifferentiated adventitial cells are fiber formers. In progressive changes, particularly in tubercles and certain tumors, Krauspe found a close relation between the vascular system and the reticulate fibers, and that they originate chiefly from cells.

Of great importance is the membrane substance closely connected with the fibers. It would really be more correct to speak of a fibrous membrane than of reticulate fibers. There are transitions from reticulate fibers into collagenous fibrils, but the nature of the transformation is not explained. In the direction of the elastic fibers, the boundary line of the reticulate fibers is not very well defined. Krauspe therefore acknowledges Ranke's theory of a living mesenchymal network and assumes a mesenchymal fibrillary tissue which is identical with Mallory's fibroglia, the reticulate fibers and the precollagenous and preëlastic fibrils. He believes that this primordial fibrillary tissue may continue as reticulate fibers, or that it may be differentiated by chemical or mechanical causes into elastic or collagenous fibers; that one and the same cell, whether it is called fibroglia, reticulum cell or endothelial cell, but which is, in short, the reticulate fiber-forming cell, is capable of forming differentiated fibrils.

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#### **Postmortem Autolysis of the Suprarenal Cortex.**

*Erik Johannes, Kraus and Luigi Sussig, Virchow's Arch. f. path. Anat., etc., 237: 265, Berlin, March 18, 1922.*

In the suprarenal cortex there are occasionally areas of different size and form without nuclei and resembling necrosis. To decide whe-

ther these changes are really tissue necroses, as apparently most authors have assumed, or whether they are postmortal autolytic changes, about 80 pairs of suprarenals were examined histologically. In 12 cases in which they were examined two and a half to nine hours after death there were no nonnucleated cortical regions. The earliest period at which such areas were found was ten hours after death; on the other hand some suprarenals did not show such changes even sixty-one hours after death. They are doubtless postmortal changes and are most likely to be found in infectious-toxin processes. No relationship could be demonstrated between the postmortal disappearance of nuclei, and the blood, lipoid and pigment content of the cortex or the tingibility of the medullary substance. This change has nothing to do with cadaverous softening of the suprarenal. The author concludes that in the human suprarenal, in addition to true necrosis, which according to his experience is not very frequent and is generally due to circulatory disturbance, changes are found which are characterized by loss of nuclei of the cells and which may simulate necrosis, but which are in fact due to postmortal autolysis. The reason for the occasional early appearance of such pseudonecroses is due not so much to a special sensitiveness of the cortical parenchyma in these cases to postmortal autolysis, but rather to a cell injury caused during life by certain toxic substances, which is responsible for an early and rapidly progressive postmortal autodigestion of the cells.

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### **The Concepts and Theories of Inflammation.**

*Aschoff, Münch. med. Wchnschr., 69: 655, May 5, 1922.*

The term "inflammatory processes" includes those which are characterized clinically by redness, tumor, heat and pain, morphologically by degeneration, exudation and proliferation, physiologically by certain circulatory disturbances, increased oxygen consumption, local immunity reactions, etc. These inflammatory processes, or in short "inflammations", of the organs and tissues are designated by the Greek ending "itis". The inflammatory reaction inherent in these processes is produced by infectious toxic, traumatic, circulatory, or defective factors, and may serve either for defensive reparative or regenerative purposes. In order to avoid confusion in the conception of inflammation, it is necessary to classify inflammations according to their inherent reactive processes from the etiologic or functional standpoint into defensive (direct) or reparative-regenerative (indirect) processes. The clinical definition of inflammation usually confines the term to the infectious toxic conditions, that is processes associated with defensive reactions. There are many theories in regard to the origin of the individual inflammatory processes, that is their etiologic connection. None of these is adequate and unequivocal as an etiologic explanation of the complicated inflammatory process. The nominal definition of inflammation, whether based on characteristics, etiology or function, should be clearly differentiated from the various theories of inflammation based on pathogenetic definitions or on the forerunner of an etiologic explanation.

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**Remarks on Felix Marchand's Critical Study of the Concept of Inflammation.**

*G. Ricker, Virchow's Arch. f. path. Anat., etc., 237:281, Berlin, March 18, 1922.*

Ricker tries to answer Marchand's objections. He rejects Virchow's cellular pathology unconditionally as anthropomorphic and desires to substitute for it a pathology of relations. He holds to his opinion that the local circulatory disturbances are caused by irritation of the vessel nerves and appear in different forms depending on the nature of the irritation. He again lays stress on the fact that the tissue changes originate and run their course dependent on the circulatory disturbances, on the ground of the changed relations caused by them between the blood and tissues. Based on his experiments he also takes up the argument against Marchand's conception of inflammation and necrosis, or rather against the fact that Marchand rejects his theory of stasis as due to the action of the strongest irritation of the vessel nerves. He demands that pathologic processes be regarded in the sequence of their causal connections, which has been shown by experience, with equal consideration of all physical processes.

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**Protoplasmic Hysteresis in the Course of Inflammation.**

*E. Vejnarova, Časop. lék. česk., 61:448, Prague, May 20, 1922.*

Under various influences in certain cases cells occur which have the form and character of young cells and vary biologically from the normal cells. Inflammation is a process that is characterized by vascular, necrobiotic and proliferative changes. The mutual relation of these changes depends on the quality and the intensity of the causative factor. Inflammation occurs as a reaction to a disturbance which may lead to exudation and proliferation. Cure results when the injurious element has been sufficiently attenuated. It is followed by formation of young and specific tissue or more frequently of granulation tissue which becomes organized into scar tissue with loss of the original function. These changes are manifested morphologically and physiologically and are accompanied by physicochemical processes.

Vejnarova seeks to determine how far protoplasmic hysteresis is involved in the process of inflammation. Experiments were made on the muscles of the posterior extremity of *Rana fusca*. Inflammation was induced by simple incision, cauterization with HCl and intramuscular injections of turpentine oil. The animals were killed in from 19 hours to 10 days and in longer intervals up to ten weeks. The inflamed muscle and a like mass of healthy muscle from the other limb were removed, triturated, mixed with distilled water and filtered; pH was determined by Michaelis's method and flocculation ability by Ruzicka's method. The results of both reactions were parallel and are presented in a curve. The H-ion concentration usually reaches its maximum on the fourth day and returns to normal about the tenth day, when it becomes and remains subnormal. Flocculation is at first retarded or occurs after the addition of more alcohol,

indicating greater stability of the albumin molecule and falling hysteresis. In later stages, flocculation becomes more rapid, indicating a labile condition of the colloids, diminished dispersion and increased hysteresis. In the early stage of inflammation, hysteresis drops to a value corresponding to hysteresis of the same tissue in a young animal. This may be considered as evidence of a return to the youthful stage, inflammation constituting a return to the embryonic stage. This condition is followed by an increase in hysteresis above normal, suggesting increased local aging (the higher degree of hysteresis corresponding to older age).

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**Histamin as an Inflammatory Agent.**

*William Bloom, Bull. Johns Hopkins Hosp., 33:185, May, 1922.*

The process of inflammation is much alike in character no matter how produced. The tissue reaction to bacteria is the same as that to casein necrosis in the absence of bacteria. This leads to the hypothesis that inflammation is caused by some specific substance present in damaged tissues. Such a substance, if it exists at all, must be a capillary poison, must be liberated through trauma and bacterial action upon proteins, and must attract leukocytes to the focus of injury. The recent fund of knowledge concerning histamin (beta-iminazolyethylamin) as a capillary poison released from all damaged tissues, led Bloom to test it for possible inflammatory action. A previous attempt of Paul to produce leukocytosis by intravenous injection of histamin in the rabbit was inconclusive. In Bloom's experiments histamin was injected intraperitoneally and subcutaneously in salt solution; it was injected subcutaneously in oil suspension, to secure slower action. Colloidion capsules containing histamin were implanted beneath the skin and allowed to remain for several hours. These experiments were controlled with salt solution and with croton oil, an active inflammatory agent. The chemotactic properties of histamin for leukocytes were tested under proper control both in vitro and in vivo, with the result that neither inflammatory inciting nor chemotactic properties of histamin could be demonstrated.

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**A Theory of Cancer.**

*Thomas Cherry, M. J. Australia, 1:425, Sydney, April 22, 1922.*

Recent experimental work has shown that chronic irritants are able to produce a type of epithelioma with such regularity that the relationship between irritation and proliferation must be considered as established. From what is known of the influence and mode of action of the internal secretions, it is probable that all growth, epithelial or other, is due to their influence. Any cells at certain phases, normal or abnormal, of their life cycle may call such secretion to their assistance, and proliferation will be the result. The author calls this internal secretion "proliferin." It has long been known that pigment in animals is for the most part formed by the interaction of an oxidizing ferment (tyrosinase) upon certain colorless chromogenic substances. If the skin of young animals or of embryos be ground up and extracted with water, the expressed

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juice, when incubated with solid tyrosin, will throw down a pigment if a trace of ferrous sulphate be added to act as an activator, but not in the absence of the activator. In albinism the skin lacks the power to secrete either the ferment or the activator. The melanotic sarcomas connect cancers with albinism. In man they affect the white and yellow races, but negroes are nearly exempt. As the cells of the tumor usurp the normal pigment function of the skin, the presumption is that a tyrosinase is present in these cells also. That is, in albino animals and light races of man, a cancer may carry on in an exaggerated form a function which is poorly developed in the tissues of the host. But when the normal cells (as in the negro and in colored horses) are well endowed with this function, the pathologic process does not occur. A second link in the chain is supplied by the changes in the mammary gland which follow conception. These are due to the action of an internal secretion of the ovary, and include a deposit of pigment in the areola and proliferation of the secreting cells. Another internal secretion inhibits the full activity of these cells until the uterus has been emptied. Quite probably it is the same secretion of the ovary which causes the pigmentation and also the proliferation. If this be so, it appears that this secretion acts by provoking the one set of cells to secure tyrosinase and the other to secure "proliferin." As an activator is required for the tyrosinase, it is possible that it is required in the other case also. An activator is known to be necessary for normal pigmentation, and if necessary for proliferation, it affords an easy solution to most of the difficulties which beset any theory of tumors. If the ordinary carcinoma of the breast were a pigmented tumor, its relationship to the normal physiologic history of the organ would have been recognized long ago.

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**Experimental Study of the Pathogenesis of Arteriosclerosis.**

*M. Schmidtman, Virchow's Arch. f. path. Anat., etc., 237:1, Berlin, March 18, 1922.*

With the aid of his method of inhibition of blood pressure in rabbits the author studied the process of alimentary and infectious injuries upon blood pressure and upon the vascular system. Rabbits were fed with dry liver, bread and a small amount of vegetables or dried muscle. By keeping this up long enough changes could be produced in the aorta and other arteries that corresponded to human arteriosclerosis. In the different animals these changes were of different degrees under the same experimental conditions. On feeding with powdered liver and vegetable diet there was a marked rise of blood pressure in rabbits, varying in different animals, in some over 30% higher than normal. The severity of the arteriosclerotic changes produced was parallel with the rise in blood pressure. On feeding with muscle powder instead of liver powder there was no such rise in pressure. As a rise of blood pressure can be brought about by cholesterin, and as other authors have reported similar arterial changes, from feeding cholesterin, that apparently is the substance in the liver powder which causes the rise in pressure; this assumption will be tested by making feeding experiments with liver freed of cholesterin. The experiments show that in the ex-



perimental production of arteriosclerosis in rabbits, in addition to cholesterinemia of the blood there is always a rise in blood pressure. Whether a chronic rise in blood pressure alone can be produced without cholesterinemia and arteriosclerotic changes the author cannot say at present, as he does not know any method of producing chronic increase in blood pressure.

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**The Circulation in the Frog's Tongue under Pathologic Conditions.**

*A. Fröhlich and E. Zak, Klin. Wchnschr., 1: 1055, Berlin, May 20, 1922.*

The circulation in the frog's tongue was observed after extirpation of the liver and kidney, after destruction of the adrenals and after phosphorus intoxication. Twenty-four hours after operation there was pronounced pallor of the ventral side of the tongue, the superficial capillary network was dilated and relaxed, the capillaries often showed varicose dilatation, there were very few erythrocytes in the capillaries and there were large accumulations of leukocytes in the capillaries and veins. There was no leukocytosis in the circulating blood and tissues. The changes in the vessel wall and in the cell distribution were not to be attributed to loss of blood; frogs treated by the aforesaid methods or intoxicated with peptone showed a rapid increase in weight, in contrast with frogs that were simply bled or those in which the spleen or ovaries had been extirpated. This is an overcompensation. The increase in weight in frogs after nephrectomy is comprehensible, as they have lost an organ concerned in water metabolism; even more noteworthy is the water retention after removal of the liver and after intoxication with phosphorus or peptone.

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**The Production of Lung Hemorrhages and Associated Phenomena in Rabbits and Guinea-Pigs.**

*Sara Elizabeth Branham, J. Infect. Dis., 30: 670, June, 1922.*

Inoculations were made with sterile physiologic salt solution and nasal washings from normal persons and persons suffering from colds, the washings having been passed through a tested Mandler filter. Guinea-pigs and rabbits were used, the latter in larger number. Of 70 animals included in the study, 32 received intratracheal inoculations. A marked change in the total leukocyte count was noted in 75% of these within 6-48 hours after inoculation. Leukopenia occurred almost twice as often as leukocytosis; and in 3 cases the leukopenia was accompanied by an acute conjunctivitis.

Of the 32 animals 16 were killed, and in the lungs of 8 (50%) striking hemorrhagic areas and a marked emphysema were observed. Of the latter animals 4 had shown a leukopenia, 1 leukocytosis, and 3 no blood change. In all, 50 of the 70 animals had been killed, at the time of the report, and in half of them marked emphysema and hemorrhages were found. These lesions occurred with equal frequency in normal uninoculated animals and in those injected intratracheally. They were not found in any animals killed with ether; they have not

been found in all animals killed by a blow on the back of the neck, and have been reported in some killed in other ways. Their occurrence in 67% of all animals killed by a blow, and in 87% of those which were held head up when the blow was given, seems to indicate that the mode of death has some association with them. There was no evidence that the association of the lung lesions with the conjunctivitis and changes in the leukocyte count was more than accidental.

No explanation of the occurrence of these lesions is offered, but it is pointed out that the fact that hemorrhages and associated phenomena are produced with considerable frequency in apparently normal rabbits and guinea-pigs killed in certain ways should be borne in mind when these animals are used for experimental purposes.

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**Sunstroke and Insolation. Chemotherapy, Hemoclasia by Heat, Acquired Defense or Immunity.**

*Charles Richet, Jr., J. de physiol. et de path. gén., 20:59, no. 1, Paris, 1922.*

The author worked with rats, mice and rabbits, exposed under glass to the sun and heated in a dry oven, or in cotton on a heated plate. The chemical rays are inactive, the effects of heating being due to the heat rays. Young, and especially newborn, animals resist heat less than adults. Adolescents resist more than full-grown animals. The heavier appear less resistant than the lighter animals, but individual variations may perhaps operate. Fasting animals do not resist heat well. Bleeding also diminishes the resistance. Ether, adrenalin, alcohol, morphin and kola do not retard death produced by heat stroke, but camphorated oil and caffein do. Hemoclastic changes may be produced, consisting of changes in the coagulation, leukopenia and lowered blood pressure. Animals do not become habituated to heat, but are rendered more sensitive to it, when the interval between heatings is less than sixteen days. If the interval is greater than sixteen days, the animals become accustomed to the heat. The habituation is in accord with that developed by man in tropical climates, and seems to agree with certain principles of immunity. Physical training, for example, probably develops an immunity to fatigue poisons. The hemoclastic changes are anaphylactic. Possibly some cases of malarial hemoglobinuria may be due to heat. The hemoclastic reactions may perhaps tend to produce cure in infections and hyperpyretic states.

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**Researches on Tissue Respiration in Avitaminosis.**

*W. R. Hess and N. Messerie, Hoppe-Seyler's Ztschr. f. physiol. Chem., 119:176, Berlin, April 20, 1922.*

The nature of avitaminosis resulting from avian beriberi is elucidated by referring the observed symptoms to insufficiency of tissue oxidation. In vitro, also different tissues of avitaminosis pigeons show pronounced respiratory insufficiency, which has been demonstrated for kidney, cardiac muscle, pectoral muscle, crural muscle and in a lesser

degree for the pancreas. Abderhalden also determined diminished respiration in vitro by means of gaseous oxygen consumption by excised tissue. The experiments were repeated with the aid of a new and improved method, respiratory intensity being determined by Lipschütz's dinitrobenzol method. As a result of oxygen consumption by the tissues a part of the combined oxygen in dinitrobenzol is split off with formation of m-nitrophenylhydroxylamin. This substance reveals itself by the yellow coloration of the reacting medium. The method was improved by accurate comminution of respiratory tissue and by employing a clear control liquid, obtained by precipitating with phosphotungstic acid, for determining colorimetric concentration. Finally, in order to obtain more exact results the respiratory tissue was freed from oxygen by displacing air with nitrogen. The standard Ringer solution was stabilized by adding one-sixth mol bicarbonate solution which yielded a constant reacting medium. The animals' age was likewise taken into consideration. Selected tissues were: kidney, liver, heart and pancreas.

The experiments amply show the difference in the behavior of healthy and avitaminosis tissue. This difference is much more pronounced, in the case of most tissues, in coarse than in fine sections. The percentage retardation is highest in the liver and brain and least in the pancreas. Kidney and heart stand between these organs but even with them the difference between healthy and diseased animals is great. The experiments show, also, that young animals are very sensitive to an avitaminosis regimen. That is analogous to the greater sensitiveness of young animals to hydrocyanic acid. Respiratory intensity was shown to depend considerably on the degree of tissue comminution as well as on the amount of buffer substances contained in the system. Control of the reaction change in the respiring system showed this process, which is conditioned by formation of acid, to be likewise retarded in avitaminosis tissue. Hess's and Abderhalden's former experiments, in the sense of strongly pronounced respiratory insufficiency, are therefore confirmed.

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**The Pigment in Chloroma.**

*B. Brahn, Virchow's Arch. f. path. Anat., etc., 237:324, Berlin, March 18, 1922.*

The treatment of bone-marrow with ammonium sulphid according to the directions of A. Kossel and G. Giese gives the same result in chloroma and in normal cases. The outcome of this reaction makes it improbable that the pigment of chloroma and that of green pus are the same.

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**Mast Cells in Pleural and Peritoneal Effusions.**

*J. Sabrazès, Arch. d. mal. du coeur, 15:214, Paris, April, 1922.*

The author has examined pathologic serous exudates of the pleura and peritoneum in a case each of tuberculous peritonitis, effusion accompanying peritoneal metastasis from tubal epithelioma, tuberculous pleurisy, pleuritic effusion containing many eosinophils (cause unknown) and

hydrothorax accompanying Bright's disease. In hydrothorax and in the exudate of acute pleurisy, mast cells rarely occur. They are more numerous and frequent in chronic or recurrent effusions of the pleura and peritoneum. Mast cells have no ameboid movement, nor are they phagocytic. In edema congestion, or inflammation of various origins they are present on the pleura or peritoneum and enter the effusion only passively and not by any motion of their own. Those observed were of the type occurring in the blood. Promast cells (as described by Sabrazès and Lafon) may occur in tissues and exudates and must not be confused with plasma mast cells. The author stains mast cells with a 1:500 watery solution of methylene-blue. The smear is first dried, but not fixed. A cover-glass, bearing a very small droplet of the methylene-blue solution, is reversed upon the smear. The basophilic granules of the mast cells stain violet, those of the promast cells pure blue. The centrifuged leukocytes are mixed and pipetted off; smears are pulled and dried. The cover-glass should be very thin.

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**Study of the Giant Cells in the Mouse's Spleen.**

*L. V. Klaschen, Virchow's Arch. f. path. Anat., etc., 237:184, Berlin, March 18, 1922.*

These studies were concerned with the origin and development of the megakaryocytes and were made on mouse embryos of 5 to 8 mm. length. In the spleen of the normal mouse megakaryocytes are very abundant and are identical with the same type of cells in the bone-marrow. The studies led to the following conclusions: (1) In embryonic life, giant cells are among the first cells differentiated from the lymphoid elements of the hematopoietic areas. (2) In postembryonic life the giant cell of the mouse's spleen develops from lymphoid tissue. (3) The nucleus of the giant cell does not as a rule develop by mitosis followed by coalescence, but by increase in volume, surface enlargement, constriction and division. (4) The protoplasm of the mature giant cell is broken up into blood-platelets as described by Wright. (5) The gigantocellular reaction caused by caseosan stimulation is especially adapted for the study of giant cell development in the mouse's spleen.

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SECTION 1

ANATOMY, PHYSIOLOGY AND BACTERIOLOGY

1a. ANATOMY AND PHYSIOLOGY

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**The Pregnant Uterus of a Gorilla.**

*L. Bolk, Anat. Anz., Jena, 55:457, June 24, 1922.*

The most striking point about the internal genitals of the gorilla is that the external form of the ovary is quite different from that of the adult human ovary but strongly resembles that of an infantile ovary. The greatest length was 37 mm., the thickness 8 mm., the breadth 10 mm. The corresponding measurements in a 22 year old woman as given by Häggström are 42, 15 and 27 mm. The difference between the corresponding dimensions in the gorilla and man is considerable. The organ is considerably smaller in monkeys than in man. Probably the somewhat different structure of the organ is responsible for this. The upper surface of the ovary in the author's specimen presented a very peculiar aspect. The greater part of the surface was thickly covered with short papillas and looked somewhat like the surface of the tongue. These papillas covered the whole of the median third of the surface. To each side of it there was a strip of smooth mesoövarian margin, and still farther laterally the strip became broader, so that at the tubal pole of the organ there were no papillas at all. The papillas were distributed in practically the same way on the ovary of the opposite side.

As to the finer structure of the ovary, the condition of the germinal epithelium was very noteworthy. It was preserved in part, which differs from all previous observations in primates, and it was preserved in just that part of the surface that was covered with villi. Where there were no papillas the germinal epithelium was also lacking. Where it was preserved it had the character of simple cubical epithelium. These ovarian villi were an entirely new phenomenon to author. This peculiar appearance of the surface of the ovary seems to be an exception in primates. The specimen examined by author came from an animal killed in freedom; any pathologic condition resulting from life in captivity can therefore be excluded. Author has no hypothesis to offer in explanation of the phenomenon. In addition to the villous covering of the surface the organ offered another peculiarity. There were no graafian follicles. The whole organ consisted—except for rests of the corpora albicantia—of dense connective tissue. Only after a long search did he find here and there in this tissue a group of a few cells which by their arrangement gave the impression of a primordial follicle. This condition was in marked contrast with the pregnant condition of the animal—the uterus contained a fetus—for the structure of the sections of the ovary resembled that of an animal no longer capable of bearing young.

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**The Action of Ultraviolet Rays on Arbacia Eggs, Especially as Affecting the Response to Hypertonic Sea-Water.**

*Ralph S. Lillie and Margaret L. Baskervill, Am. J. Physiol., 61: 272, July 1, 1922.*

The authors exposed these eggs to the rays from the mercury arc in flat-bottomed vessels in a shallow layer of sea-water, the lamp used and the conditions of experimentation being the same as those described in the authors' recent paper on starfish eggs. The experiments showed that brief radiation with ultraviolet rays produces in unfertilized eggs effects similar in kind to those caused by mechanical treatment, exposure to lipoid-alterant compounds or high temperature, or the action of unbalanced salt solutions. All of these agents appear to act by producing structural changes in the egg system, primarily in the surface layer; as a secondary physiologic consequence the responsiveness of the egg to hypertonic sea-water is increased. There appears to be nothing specific in the effects produced by radiation. The energy of the absorbed rays is locally transformed, and the resulting structural and other changes in the protoplasmic system are similar to those produced by other physical agents and have similar physiologic effects.

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(1a—83)

**Histologic Notes.**

*Max Clara, Anat. Anz., Jena, 55: 399, June 3, 1922.*

*Ciliated Epithelium in Ducts of Glands of the Uvula.*—The presence of cylindric ciliated cells in the outlet ducts of the glands on the nasal side of the human uvula has often been noted before. The distribution of the ciliated cells is highly irregular; in many places great numbers of them are to be found together, while in other areas only individual ciliated cells are to be found. The ciliated cells seem to be somewhat larger and clearer than the surrounding nonciliated cylindric cells. The nucleus is round, poor in chromatin with a large oxyphil nucleolus and looks like a clear vesicle; it is somewhat larger than the nucleus of the ordinary cylindric cell, which is a longer oval and which contains one or two smaller oxyphil nucleoli. It also lies farther toward the base of the cell, so that the greater part of the cell plasma is turned toward the lumen. The plasma stains brighter with eosin and there is an almost colorless ring around the nucleus. By these staining peculiarities of the plasma and the position of the nucleus in a deeper layer of the epithelium, these cells can easily be distinguished from the other cells aside from the fact that they are ciliated. No beaker cells can be seen in the outlet ducts. Between the ciliated cells there are sometimes small, darker staining cells with dark elongated nuclei, such as often occur in stratified ciliated epithelium, which are possibly compressed cells. Leukocytes are frequently found migrating through the epithelium.

*Free Langerhans Cells in Connective Tissue of Pancreas.*—The observations were made on the pancreas of a man who had died of encephalitis. In one place the collections of cells were found lying free in the connective tissue; some of the islands were very clearly surrounded by a concentric layer of connective tissue. In some of the secretions there were groups of large outlet ducts which were distin-

guished by an especially high cylindric epithelium, large lumina and by pronounced contortion and branching. The islands were always found near these outlet ducts lying free in the connective tissue. The islands themselves did not differ in structure from those found in exocrin gland tissue. In some of the islands author could see an immediate connection with small outlet ducts, as a process resembling a pedicle, with a lumen projected from the duct and passed in a semi-circular form to the island. The epithelium of this duct was low. Author believes that for some unknown reason there had been an atrophy of the end of the gland followed by connective tissue proliferation, in which the outlet ducts had been preserved and even proliferated. As most of the Langerhans islands lying in the connective tissue showed no connection with the outlet ducts, author assumes that the majority of them originally lay in other gland tissue and that being more resistant structures they were preserved as well as the outlet ducts. But the fact that in some places the islands were connected with outlet ducts indicates that some of the islands had been newly formed by regeneration from the outlet ducts as is asserted by Weichselbaum and Kyrle. However, as these changes were only demonstrated in a circumscribed area and the rest of the pancreatic tissue was completely normal (no connective tissue proliferation), and as the cadaver showed no other pathologic conditions of the digestive tract, it may be assumed that these purely local changes are not to be regarded as pathologic, and probably have a certain analogy with those processes in the liver which lead to the formation of the so-called aberrant vessels.

*Structure of Helicine Arteries.*—The helicine arteries of the corpora cavernosa of the penis are nothing but a direct emptying of small arteries into venous spaces. Author demonstrated epitheloid modification of the musculature in them, which however was not distinct everywhere. The surrounding connective tissue in most cases was arranged in several layers around the anastomotic vessel. The helicine arteries for the most part lie on the urethral side of the deep artery of the penis. They bring about rapid filling of the cavernous blood spaces. When these are full of blood the helicine arteries close and prevent the blood flowing out.

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### **The Significance of Physical Characteristics of Cartilage in the Vital Staining of Cartilage.**

*Richard Lotzin, Anat. Anz., Jena, 55: 369, June 3, 1922.*

The results of vital staining with trypan-blue in adult joints are reported. Periosteum and joint capsule always showed pronounced granular staining, especially in the vessel endothelium. Moreover the lining of the synovial folds and villi, rich in cells, showed a striking storing of stain. Also the remaining boundary of the inside of the joint showed strong vital staining. There seems to have been a considerable transportation of stain into the joint cavity. The inner layer of joint cartilage, which is adjacent to the bone, was not reached by stain from the marrow cavity, for there was not a trace of coloring in its cells. This is partly due to the complete absorption of the stain by the bone cells lying in front of it, which store the stain, and partly, also, probably, to the practical impermeability of this part of the matrix

to trypan-blue. There is a striking correspondence in the zones which contain vitally stained cartilage cells and those parts whose matrix is stained metachromatically with safranin, as for example the inner joint cartilage layer.

With reference to the disputed question among histologists as to whether the staining is to be explained on physical or chemical principles, author believes that chemical properties both of the cartilage and the stain help to determine the conformation of the vital staining as well as its diffusion in the matrix, but that the presence of physical differences in density may also aid in the interpretation of vital staining of cartilage. At any rate author showed by experiment that the matrix of the marginal cartilage and joint cartilage is more readily permeable by the stain than the central cartilage.

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### **The Secondary Naphthol Reaction.**

*W. Loele, Folia Hematol., Leipsic, 27: 181, May, 1922.*

The naphthol reaction is employed for demonstration of secondary aldamins and aldaminic acids. It is necessary that there be primary aldamins which are influenced by the aldamins of *Limax* and *Arion*. Author studied the influence on *Limax* and *Arion* of various reagents in order to get different points of view on the reaction. The results showed that *Limax* preparations, hardened in alcohol, showed no distinct reaction of the mucous cells and that sections placed in formol showed an intense black staining of the granules in naphthol. The secondary reaction becomes positive if other frozen sections from man and animals are placed with the section of snail.

Author recommends the following methods for the demonstration of the naphthol reaction: Only large snails collected from May to the middle of July should be used; they should be immediately killed in 20% formalin and then conserved in 10% formalin. Thick specimens should be treated previously with fumes of ammoniac. The solution of formol must be free from acids or the acids may be removed by addition of  $\text{CaCO}_3$ . Formol fixation is necessary for the demonstration of the nucleolus. The naphthol should be concentrated in a concentrated caustic solution, in which snails, after being fixed in formol, are placed. The sections are useful for further examination if the nucleoli are visible in 3-6 hours. The snails are then cut in frozen section and the sections are placed in the same dish. They are placed in the naphthol solution after 6-12 hours. The nucleoli of the lower sections soon become stained black if the ferments of the snails are effective.

Of all tissues showing the secondary reaction with *Limax* and *Arion*, the most important are small and large lymphocytes (old leukocytes give no reaction), vascular endothelium, renal parenchyma, liver, epididymis and salivary glands. A pretty reaction is seen in the nerves, sexual cells and pathologically changed tissues such as typhoid lymphoma, fibro-adenoma of the breast, myoma of the uterus, various carcinomas, melanoma, glioma and sarcoma. The secondary naphthol reaction is also seen in plasma structures in bone, cartilage, elastic fibers, hyalin, pigment containing iron, mucus and Altmann's granules of the renal epithelium. The red cells in the smaller vessels stain black

but the reaction is negative in the larger vessels. The secondary naphthol reaction was also found under the influence of various aldamins (in addition to those of *Limax* and *Arion*) of the plant kingdom as in elder, white syringa, asparagus and potato. Conclusions are that the primary reaction in the protoplasm is negative if the secondary reaction in the nucleus is positive; that primary granules appear in the protoplasm if the naphthol bodies are absent; that the primary reaction is negative if the secondary granules escape from the nucleus into the protoplasm.

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#### **The Pericardiac Cell of Insects.**

*A.-Ch. Hollande, Arch. d'anat. micr., Paris, 18:85, May 15, 1922.*

Author has examined a number of insects of the groups Thysanouria, Orthoptera, Neuroptera, Hymenoptera, Coleoptera, Lepidoptera, Diptera and Hemiptera. The living cell may be studied by placing it in a drop of the insect's blood under the cover-glass. Insects may be injected with aniline dyes, natural colors, proteins, organic salts and mineral compounds. The various products may be mixed with the insect's food or saliva. Five per cent. solution of ammonium carminate is especially valuable. Author has used practically all the ordinary stains.

The pericardiac cells of insects are located about the cardiac sinus; they may be localized in its wall and occupy the interior of the pericardiac space. When but few, the cells are very large; when many, they are medium or small. They are usually discrete, but may unite to form a tissue. They are supported by fine connective tissue fibrils, by means of delicate protoplasmic membranes. The fibrils originate in the cardiac adventitia. The appearance of the living cell varies with age and other biologic conditions. There are usually one or more large, central vacuoles, regular, and usually circular, in outline. Toward the cell-borders there are fine vacuoles, sometimes outlined by special protoplasmic strias composing peripheral absorption cones. Between the two extremes, there are medium-sized vacuoles. The vacuolar liquids usually contain pigment (yellow, red and green).

The pericardiac cell is mesodermic. The nucleus divides in the very young larva by mitosis or simple change to form several secondary nuclei. As the outer larval covering is shed, the small pericardiac cells located near the hypodermic tissues produce new cells. The direction is away from the heart. The large cells are thus near the heart, the smaller ones more remote. The cell is a glandular closed cell having a merocrine secretion, formed in the small, peripheral vacuoles. The secretion is acid and collects in the center of the cell in large vacuoles. One or two nuclei are usually present. If two, the cytoplasm sometimes tends to collect in semi-independent masses about each nucleus, which become separated by a sort of septum. The external cell membrane is not well developed. The cells continue through the metamorphoses unless killed during the larval stage by absorbing toxic substances, such as injected ammonium carminate. In this case they are disposed of by phagocytes. The cells are very absorbent. On the approach of the metamorphoses, changes occur in the pericardiac cells, varying with the insect species, such as the formation of several new nuclei or protein inclusions.



The vacuolar liquid consists of water, lipoids, pigment and acid substances. The pigment is derived from the blood and has the same origin as the blood pigment, except where extraneous pigment in the blood is taken up by the cells. Thus brown pigment, in some Lepidoptera, undergoes several changes, becomes the red body, is discharged into the blood and absorbed by the pericardiac cells. Melanin derived from phagocytosis behaves similarly. The capacity of the cell to absorb colloids (albumins, albumoses, globulins) is remarkable. Crystalloids rarely enter. Iron and other elements may enter if combining with colloids or united to them by adsorption. Natural colloid colors are taken up easily. The cell absorbs aniline colors selectively. The molecular composition of the stain has much to do with its absorbability. The pericardiac cells are not renal or renal accumulators, as often believed. They can transform ammonium carminate into pure carmin. The persistent red color is due to the insolubility of the carmin, which therefore remains. Waste products do not accumulate in the cells. The acid substance of the cell is a true secretory product, and required for diastatic reactions and for neutralizing alkaline substances taken up from the blood. Complex colloid molecules are split by the cell. Proteins are digested and finally disappear. Colloids are thus gradually changed to crystalloids, which increase osmotic tension and cause osmotic changes. The power of absorption of the cell varies directly with the activity of its diastases.

Substances absorbed by the cell come into contact with the small peripheral vacuoles, are immediately attacked by the cell ferments and the resulting compounds, together with other substances secreted by the cell, compose the content of the large central vacuoles. Comparisons with vertebrate cells are rash, biologically speaking. Nevertheless, if the pericardiac cells be so compared, their vertebrate analogues would be the hepatic, and not the renal, cells. Naturally, many hepatic functions, such as the glycogenic function, do not exist in the pericardiac cell. However, the pericardiac, like the hepatic, cells, encounter digestive products freshly poured into the blood; they take up incompletely digested proteins; neutralize excess of alkali; destroy oxidized substances; probably destroy toxins and constitute a factor in immunity, and, finally, they secrete special substances which circulate in the blood.

Decomposition products resulting from the action of the cell ferments, unless utilized by the organism, are excreted by the malpighian tubes, the true insect kidney. The biochemic function of the pericardiac cells is thus very important in the life of the insect.

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### **The Minute Structure of the Purkinje Fibers in the Hearts of Birds.**

*E. H. Tang, Anat. Anz., Jena, 55: 385, June 3, 1922.*

In the subendocardial connective tissue of birds (doves, crows, owls) there is a network of Purkinje fibers which is the end distribution of the atrioventricular bundle. The fibers penetrate with the blood-vessels from the subendocardial connective tissue into the myocardium and pass gradually into heart muscle fiber. The fibers are made up of cells in which granular mitochondria are found, which



gradually become transformed into vesicles and then disappear. In addition to the mitochondria there is a Golgi's network closely surrounding the nuclei. The findings do not at all confirm the theory held by many authors that Purkinje's fibers are structures that have remained in an embryonic condition, and that form a matrix for the permanent new growth of heart muscle fibers. The chief argument against this theory is the entire absence of figures showing division of nuclei, nor does the finding of mitochondria argue in favor of this theory. On the other hand everything indicates that Purkinje's fibers are only a specially modified part of the conduction system.

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**The Capillaries of the Bone-Marrow of the Adult Pigeon.**

*Charles A. Doan, Bull. Johns Hopkins Hosp., 33:222, June, 1922.*

Detailed knowledge of the finer circulation in the bone-marrow is very important because of its connection with blood-cell formation. At present there are 3 theories: (1) that marrow blood spaces are lined by parenchyma alone, without endothelium; (2) that there is an entirely closed vascular system; (3) that there are endothelial vessels with openings directly communicating with the parenchyma. Doan has studied the marrow of pigeons, which for the sake of microscopic clearness he has depleted of free cells by starving the birds. He describes the circulation as consisting of an arterial tree fed by the medullary artery, some arterioles from the shaft periosteum, and a few from the extremities of the bone. The venous tree is similar, beginning in large sinusoids which are very numerous. A few capillaries of the usual type connect the arterioles with these larger venous sinusoids. However, there exists also, as Doan here describes for the first time, a very extensive bed of collapsed endothelial tubes, as a network communicating with the other marrow-vessels at many points. India ink can with difficulty be forced through the narrow lumina of this network, which has closed walls, so that there are no openings into the tissue-spaces. This hitherto undescribed endothelial network closely resembles the embryonic vascular plexuses which Sabin has found to be the source of all types of blood-cells. Its presence in the adult marrow is presumably related to the blood-forming function of the marrow.

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**Isolated Plethysmography of Both Heart Ventricles.**

*P. Wolfer, Arch. f. exper. Path. u. Pharmacol., Leipzig, 93:1, May 2, 1922.*

The experiments were made on rabbits under urethan anesthesia and artificial breathing. Carotid pressure curves were recorded by the introduction of the blood pressure cannula. The sternum and ribs were removed and the 2 halves of the heart were surrounded by 2 light aluminum loops, the movements of which were transmitted by means of a lever and registered on kymographs.

*Results:* (1) Pilocarpin causes dilation of both heart ventricles in systole and in diastole. The systole is only one-fifth as long as the normal systole, and at the same time there is a marked decrease in heart

action. This results in a venous disturbance in the greater circulation and a fall of blood pressure in the carotid. (2) Pituglandol causes a decrease in the systole of both ventricles, a decrease of pulse frequency and arhythmia (extrasystole). The blood in the carotid often increases by contraction of the peripheral vessels while the pressure in the pulmonary sinks. (3) Adrenalin causes contraction of the peripheral vessels by overfilling of the right ventricle with larger minute volume. The pulmonary vessels yield, the lungs serve as a reservoir, the pressure in the pulmonary rises. By the accumulation of blood the left ventricle, which on account of the contraction of the vessels has to overcome a greater resistance, is disburdened. Adrenalin also stimulates the myocardium which is often shown in a pronounced increase in the volume of both ventricles. (4) Imidazolyethylamin in small doses causes an increase in volume of the right ventricle by overdistension, on account of which the volume per beat of the left ventricle is decreased by a relaxation of the vessels of the greater circulation; by a decreased flow into the left ventricle, and by a direct injury of the heart. The vessels of the lung contract, which causes the right heart to become insufficient and the carotid pressure falls still more from lack of blood. (5) Experiments with the digitalis group were made with digalen intravenously. It causes increase of the systole of both ventricles and an increase of the volume per beat. (6) The strophanthin experiments were made with strophena zyma (1 c.c.=0.001 gm. active substance). The lethal dose is 0.3-0.4 mg. for a body weight of 2-2.5 kilos. With toxic doses, the diastolic filling remains unchanged, whereas the systoles become smaller. Heart flutter and arrest of heart action follow. In strophanthin there is only a slight difference between the therapeutic and toxic doses.

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**Effects on the Circulation of Changes in the Carbon Dioxide Content of the Blood.**

*H. H. Dale and C. Lovatt Evans, J. Physiol., London, 56: 125, May 15, 1922.*

In the authors' experiments cats were used. Some were anesthetized with urethan or paraldehyd, others decerebrated under chloroform or ether. The arterial pressure was studied when the animals' lungs were excessively ventilated with pure air and with expired air. It was found that the arterial pressure of the purely spinal cat, which is maintained under gentle but adequate artificial respiration at a high level (160 mm. or higher) is depressed by excessive ventilation with pure air, and recovers when expired air is substituted, in the same manner as that of the anesthetized cat with brain and bulb intact. On the other hand, if the spinal cord is destroyed, the small arterial pressure remaining is affected in the opposite direction; excessive ventilation with pure air now causes a small rise of pressure, while a change to expired air causes a fall.

The authors inquire: (1) Through action on what organ is the collapse of the arterial pressure produced? (2) What is the exact nature of the chemical change which produces it? Regarding the first query, since the output of the heart is not significantly reduced, neither the rhythm and force of its beat nor the filling of its chambers by

the venous inflow being affected to such an extent as to contribute materially to the fall of arterial pressure, the cause must be located in the peripheral blood-vessels and the effect must be due to reduction of the peripheral resistance, by relaxation of the normal tone of the arterioles, or of the capillaries, or of both. This deduction is supported by the changes of volume shown by a limb or a loop of intestine, enclosed in a plethysmograph. The fall of blood pressure caused by rapid ventilation is accompanied by a swelling of the organ, which shrinks again as the pressure rises, when expired air is substituted for pure air.

In the cat with the cord recently severed in the neck, the spinal centers have an efficiency in maintaining vascular tone greater than usually supposed. Provided this tone is maintained, whether by the bulbar center or by the centers of the cord, excessive ventilation will depress it; replacement of carbon dioxid in the system will restore it. When these are gone, what remnant of tone the decentralized vessels retain is increased by excessive removal, depressed by reintroduction of carbon dioxid. In discussing the second query (the nature of the chemical change) the authors found that mere changes in the pH of the blood-plasma did not produce the phenomenon in question. Variations of reaction within wide limits may be produced, with surprisingly little effect on the state of the circulation, provided the changes are effected by adding fixed alkali or fixed acid to the blood. The phenomena observed are due to abstraction and replacement of free carbon dioxid, and not to changes in the pH of the blood.

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**Studies on the Physiology of Capillaries. III. The Innervation of the Blood-Vessels in the Hind Legs of the Frog.**

*A. Krogh, G. A. Harrop and P. Brandt Rehberg, J. Physiol., London, 56: 179, May 16, 1922.*

In the authors' experiments the frogs used were narcotized with urethan and curare was given later when necessary. The forms of stimulation employed were mechanic, electric and chemical. The authors studied: (1) the effects on the vessels of stimulating the peripheral ends of the different fibers supplying the skin and the muscles of the hind legs; (2) the effect of section and degeneration of these fibers upon the state of the vessels, the local reactions and the effects produced by stimulation in the sciatic of the remaining fibers; (3) the effect of cocain on the local reactions, and (4) the existence or non-existence of true vascular reflexes causing changes in the caliber of vessels and in the circulation at and about the point stimulated.

It was found that the capillaries and arteries in skin and muscles of the hind legs in frogs are innervated through sympathetic fibers from the ninth and tenth sympathetic ganglia, which maintain the vessels in a state of (variable) tonic contraction. Stimulation of these fibers caused contraction. The arteries and many capillaries in the skin and likewise a number of vessels in the muscles are innervated through posterior root fibers the stimulation of which causes dilatation. There was no evidence of stimuli passing from the spinal cord through posterior root fibers to the vessels. Some arteries and capillaries in muscles appeared to be innervated through anterior root fibers uncon-

nected with sympathetic ganglia. Stimulation of these is followed by slight dilatation.

The local reactions of skin vessels (arteries and capillaries) to mechanic and certain chemical stimuli are due to axon reflexes along the terminal fibrils of sympathetic and posterior root fibers respectively. They are not influenced by section of the corresponding nerve stems or roots. They are inhibited to a certain extent by degeneration of the fibers, but regeneration takes place independently of these. Chemical stimulation of a single spot in the web produced dilatation over the whole web independently of the central nervous system, and it is possible that the existence of extensive networks made up of the terminal fibrils belonging to fibers of the same category and probably in connection with local nerve cells accounts for the phenomena observed.

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**Observations on Augmented Salivary Secretion.**

*G. V. Anrep, J. Physiol., London, 56: 263, May 16, 1922.*

In this paper Anrep takes issue with Langley, who in 1889 described an augmented salivary secretion which he believed was due to an increased irritability of the salivary gland to impulses reaching it. Anrep performed his experiments on anesthetized dogs and studied the effect of filling the ducts of the salivary gland; the effect of atropin; the effect of the sympathetic upon the ducts of the gland; the effect of massage of the gland. He comes to the conclusion that there is no ground for the explanation of the augmented secretion being due to an increased irritability of the salivary gland to impulses reaching it by the sympathetic nerve. Anrep suggests that the augmented effect of the sympathetic is an emptying of the gland of stagnant saliva caused by a narrowing of the ducts either due to their own contractility or due to a contraction of tissues around the alveoli and the ducts. He believes the most probable explanation of the disappearance of the augmented effect is the absorption of the saliva from the ducts and alveoli.

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**The Metabolism of the Salivary Glands. II. The Blood Sugar Metabolism of the Submaxillary Gland.**

*G. V. Anrep and R. K. Cannon, J. Physiol., London, 56: 248, May 16, 1922.*

The authors' experiments were made on dogs anesthetized with C. E. mixture, without previous injection of morphin. Chemical examination of the blood before it reached and after it left, the animal's submaxillary gland was made. In every case there was a disappearance of sugar from the blood in its passage through the gland. In the resting condition, since there is no disappearance of the fluid from the blood either in the form of saliva or lymph, the whole difference between the arterial and the venous blood sugar may be taken to represent the amount of sugar consumed by the gland. The mean rate of blood sugar consumption varied but the authors found the average figure to be 2.1 gm. per hour. Pilocarpin increases the blood sugar consumption. Atropin, however, does not change the blood sugar consumption of the resting gland.

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**Consciousness and Secretions.**

*Laurence W. Cole, Colorado Med., 19:127, June, 1922.*

One of the most interesting discoveries resulting from Pawlow's studies of the salivary glands of dogs was that different kinds of saliva are secreted by different stimuli. When the animal was given table salt or quinin sulphate, the saliva flowed immediately, was abundant, fluid and poor in ferment. For sugar or sand the saliva was slow in coming, small in amount, viscous and rich in amylase. For meat the secretion was small in amount but rich in chemical composition. This is interesting to the psychologists, since the odor of the food, the signal which has been associated with a given food, will produce the appropriate saliva. Unless reflexes are discriminating, the dog's memory of odors or his memory of the sight of a tube of quinin—in a word, his consciousness—must be the cause of the different secretions. If a dog which always preferred bread to meat, or cooked meat to raw, were confronted with 2 of these foods, the saliva would be that for the kind of food the dog preferred. Here it seemed that his desire or preference was a member of the chain of organic events.

Pawlow performed a still more decisive experiment to show the effect of consciousness on secretions. He sectioned the esophagus of a dog above the heart and made it open through the skin. Then he made a gastric fistula. After recovery, food which was placed in the dog's mouth was chewed, swallowed and discharged through the esophageal fistula. Pawlow called this a fictitious repast. A slight reflex gastric secretion could be obtained by introducing food directly into the stomach. When, however, the animal was allowed to smell a morsel of food, or food was given him to be tasted, chewed, swallowed and digested, there was an immediate abundant gastric secretion. Yet, the French physiologists say, there is neither a sensory reflex path nor a sympathetic one uniting directly the glands of the mouth or esophagus to those of the stomach in a dog whose gullet has thus been sectioned. In this case the state of consciousness is not linked with the reflex, but must be the cause of the gastric secretion. The excitation is central and linked with an emotion.

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**The Influence of Secretin Solutions on Intestinal Motility.**

*Katsumi Haramaki, Biochem. Ztschr., Berlin, 129:128, April 19, 1922.*

Solutions of organic and inorganic substances (whose active principle has not been isolated or defined) that influence intestinal movement when administered subcutaneously or intravenously find application in medicine. When these solutions are derived from body material one speaks of hormones as the carriers of the physiologic effect and designates them specifically as peristaltic hormones and thus ranges them alongside the secretins which may be, likewise, prepared from body material and which influence secretory processes.

A series of experiments were carried out in which reliable secretin solutions were tested simultaneously for their peristalsis-promoting action. The experiments yielded the following results: Following intravenous injection into the auricular vein in the abdominal-fenestra



rabbit, histamin, whey-secretin, or spinach-secretin induced distinct intestinal peristalsis in suitable doses, especially in the small intestine, and to a lesser degree in the large intestine. Decoctions of roasted barley had slight and uncertain success. Injection of 1% sodium chlorid solution corresponding in amount to that of the secretin solutions showed no action whatever. In the positive experiments peristalsis set in about 2-3 minutes after injection, the effect persisting 20-30 minutes. Thereafter intestinal movement weakened and finally the intestine returned to the state of rest which it displayed before injection. It is known that histamin stimulates smooth musculature directly. The rapid super-vention of persistalsis following injection of the aforementioned substances indicates that here, too, a primary influence of chemical substances on the intestinal motor apparatus is involved and that the motility is not incited secondarily by the filling of the intestinal lumen with secretion. The strongest peristaltic action was displayed by histamin; spinach-secretin solution came next and the weakest was whey-secretin solution in the doses employed.

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**The Rôle of the Activators in the Formation of Toxic Split Products in the Intestinal Contents.**

*A. von Wassermann and M. Ficker, Klin. Wchnschr., Berlin, 1:1159, June 3, 1922.*

Neuberg has shown that nearly all reducing substances may play the rôle of activators in fermentation of yeast. The authors examined the effect of such activating bodies on the production of toxic substances by intestinal bacteria and could demonstrate a very toxic substance for the mouse in a culture of the Fraenkel bacillus, which is wide-spread in the intestine, when placed in a 2% glucose boullion. The production of this toxic substance was greatly increased in this instance. The addition of activators increases the toxicity by 30-40%. The toxic substance has a strikingly critical threshold value. The filtrate is much more toxic than the complete culture. Filtration apparently produces a biophysical solution of the smallest protoplasm particles which are especially effective. The addition of small quantities of this filtrate to a complete culture acts as an activator similar to the d'Herelle phenomenon. The effect of the activators may be determined by all fermentation excitants and with the colon bacillus. It does not seem to be limited to fermentation quantities but the presence of carbohydrates is always necessary.

The authors assume that similar processes are at the base of intestinal auto-intoxication. It is not a matter of new bacteriologic infection but of activation and formation of toxins. This would explain the normal bacteriologic finding and the favorable effect of mechanical emptying of the intestine in contrast to the failure with intestinal disinfection. The toxin with the anaphylatoxin without incubation and which is increased by activation reminds one of the anaphylactic group of diseases in which toxic stimuli are the active cause, vagotonia, exudative diathesis and arthritism in which the products of breaking down of administered molecules of albumen play an important part. The authors recommend that their assumption be tested experimentally.



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**Animal Calorimetry. XXI. The Influence of Morphin upon Heat Production in the Dog.**

*Alfred Chanutin, Graham Lusk and James Evenden, J. Pharmacol. & Exper. Ther., 19: 359, June, 1922.*

Two dogs reacted differently to doses of 12-20 mg. morphin per kilogram body weight; one, which remained absolutely quiet in morphin sleep, showed during the second hour after treatment an average fall in the heat production of 11% below the basal level, for the third hour 6%, for the fourth hour 4%. The average reduction for all the periods was 6.2%. The respiratory quotients were unchanged by administration of morphin. In a typical experiment, the heat production was 0.6 calorie per hour less than the basal value of 16.6 calories, but the animal lost from its body to the calorimeter 6 calories per hour, or 32% more than it produced. The decrease in heat production cannot therefore be the cause of the fall in body temperature. There was no abnormal condition in the division of heat loss as between radiation and conduction and the evaporation of water.

The other dog manifested increased irritability with heightened reflexes after administration of the drug. The basal metabolism increased by an average of 10%. The maximum increase was 23% after administration of morphin, ether and chloroform. The respiratory quotients were higher after morphin was given to this dog, perhaps due to the preference of the active muscle for carbohydrate. The increase in the metabolism of this irritable dog did not prevent a loss of body heat and consequent fall in body temperature after morphin. The pathways for the distribution of the heat loss were relatively unaltered. In one experiment when morphin, ether and chloroform were given together, there was no change in the body temperature.

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**The Biologic Appraisal of Foods.**

*L. Berczeller, Biochem. Ztschr., Berlin, 129: 217, May 3, 1922.*

Experiments are in contemplation regarding the rôle of salts in nutrition, on the grouping of proteins according to whether or not they contain all amino-acids requisite for building up of animal proteins, and on the theory of accessory foods. Attempts were made to feed the animals monotonously on carbohydrate and fat mixtures, namely on starch mixtures, oil mixtures, tallow mixtures, butter mixtures and paraffin oil mixtures. The duration of total and partial hunger is determined by those constituents of the diet that are not stored by the organism. Regarding salts, it is known, as shown by researches on chlorin, calcium, phosphorus and iron, that the deficiency phenomena cause striking functional disturbances in the organ in whose building up the respective element plays an important part. Chlorin deficiency produces incomplete secretion of gastric juice; calcium and phosphorus deficiency diminish bone substance, and iron deficiency reduces the hemoglobin index. In reference to the necessity for amino-acids in human food, Henriquez and Hansen consider lysin, and Willcock and Hopkins consider tryptophan as indispensable. According to the theory of accessory factors, besides qualitative protein fat, carbohydrates and

salts, three factors are requisite, namely, the water-soluble antiberiberi vitamin, the fat-soluble antirachitic vitamin and antiscorbutic vitamin.

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**The Rôle of Specific Varieties of Proteins in Nutrition. Legumes.**

*L. Berczeller, Biochem. Ztschr., Berlin, 129:239, May 3, 1922.*

Feeding experiments were carried out to determine the duration of life in animals fed on bean flour, pea flour and lentil flour. In an analogous manner there were fed also raw peas, beans and lentils, as well as those foods inactivated by heat. The gain in weight and the time of the maximum weight were recorded. On raw beans the animals died in 5 days, and on inactivated beans in ten days. Animals fed on peas and lentils lived considerably longer. On inactivated lentils life persists 131 days and on raw lentils 276 days; on raw peas 23 and on inactivated peas 58 days. The experiments show that different legumes differ greatly in their biologic value. The cost of the legumes runs parallel to the maintenance value. Monotonous leguminous nutrition produces characteristic changes in the animal organism (illness). Males generally live a shorter time than females on legumes. The active legume effect is related to the protein quality. The effect of heat is the greater the stronger the protein action, but the former cannot be referred to a single cause. In the case of beans and peas inactivation by heat leads to relative lengthening and of lentils to relative shortening of life in monotonously fed animals.

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**The Rôle of Taste (Instinct) in Nutrition. Legumes.**

*L. Berczeller, Biochem. Ztschr., Berlin, 129:251, May 3, 1922.*

The gratifying constituents of the diet are of the highest functional importance for gastric digestion and their action extends not merely to the secretory process, but also to quality and quantity of the secreted gastric juice. Experiments showed that animals prefer death by starvation when they do not obtain the customary food, or that they reject a food offered for too long a time. In monotonous nutrition experiments the animals restricted, or even refused, ingestion of food before they became affected by the consequences of monotonous diet. The part of instinct represented by taste determines the quality of the food taken, just as appetite (feeling of hunger) determines its quantity. Researches were undertaken to determine how the animals' nutrition depends on their taste and how the animals' taste depends on the previous nutrition? The experimental animals were 3 male and 3 female white rats, which were kept separated. The animals selected the food, up to a certain point, with regard to the duration of their life. Rats nourished with lentils and peas select their food quite typically. They do not feed only on one food even if this, in itself, would prolong their life the most. At the beginning of the experiment, but particularly when their life has become endangered by prolonged monotonous experimental feeding, the animals select the biologically best food, namely, the one on which they would live longest if fed exclusively on this.

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The animals endeavor to effect a change in their food. In the course of an experiment habituation to a food that was at first rejected was observed. The course of this habituation is typical. On an average the animals ingest in each gram of food the same maintenance value although this value may be smaller than that corresponding to the optimum food. They make a selection from beans, peas and lentils in the same way as when one of these is offered with an additional food. In this case, also, the animals' duration of life is graduated in the same order as in animals fed solely on legumes. Life is longest on lentils and shortest on beans. Beans diminish duration of life in young animals considerably, even if they are fed with maize in addition to another food, though they take minimum quantities in this case.

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**Bread Cereals.**

*L. Berczeller, Biochem. Ztschr., Berlin, 129:270, May 3, 1922.*

Similar researches to those undertaken with legumes were carried out with different bread cereals. Some animals were fed a monotonous diet and others received the various cereals, partly in the form of grain and partly as flour. The selective experiments were carried out with grains of wheat, rye and maize on 3 male and 3 female rats. If rats be permitted to select from barley, rye and wheat flours, three successive periods may be distinguished corresponding to the flour of which most was consumed: (1) barley period, (2) rye period and (3) wheat period. At the end of the experiment, the consumption of wheat was larger than that of the other two foods, though the animals consumed more maize than wheat flour as soon as the grain was replaced by the corresponding flours, as was done in the first experiment. In the second experiment the consumption of the species of food corresponded to human experiences so far as the experimental animal was subject to the same alteration of taste within the experimental period as man is during his development. In both the transition from barley as the chief constituent of their diet to rye and from the latter to wheat was observed. In both experiments the animals tended more and more toward a one-sided nutrition. The quantitative course of individual feeding periods exhibited simple regularities in regard to duration as well as the amount of food consumed. The total quantity of the ingested food diminished in both experiments with increasing duration. In the second experiment (barley, rye, wheat) the animals' duration of life depended on the average daily ingestion of food. And in both experiments the two sexes showed striking differences in ingestion. The females showed a preference for rye. In the second experiment, the average ingestion of food was greater on the part of females than on that of males.

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**Investigation of the Milling Process.**

*L. Berczeller, Biochem. Ztschr., Berlin, 129:289, May 3, 1922.*

By the milling process the seeds, for instance of the pea, are altered, their flour acquiring a bitter taste. Maize ground with the germ also yields a perishable flour. This is due directly to the presence of the

germs which assume a bitter taste only in the ground state. As rice loses vitamins through dehusking, it could be assumed that the loss of bran in the milling process also results in loss of vitamins. A series of experiments were carried out with (1) wheat grain and fine wheat flour; (2) rye grain and 80% milled rye flour; (3) wheat grain, fine 70% wheat flour; and 15% bran; (4) wheat grain, artificial wheat grain from fine wheat flour and fine wheat flour; (5) wheat grain, artificial wheat grain from 95% wheat flour and 95% wheat flour. Cereals as well as legumes are affected materially in a biologic sense by the milling process. That bran is altered by milling may be concluded from the followings facts: The animals eat less of ground bran than of unground bran part of wheat grain (wheat grain, flour and bran experiment). The animals prefer, for a time at least, the artificial grain prepared from fine flour to the natural one, and the latter to that prepared from flour containing bran. But the experiments also show the imperfection of fine wheat flour as against wheat grain. A similar refusal of bran is observable in rats, as in man. All these experiments demonstrate that the animals, in course of time, recognize or learn the properties of the food. In the case of cereals the fluctuations in the finer differences are, however, less than in legumes.

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**Examination of Soy Flour.**

*L. Berczeller, Biochem. Ztschr., Berlin, 129:313, May 3, 1922.*

Soy beans contain approximately 14% protein and 20% fat, besides soluble carbohydrates. The preparation of a palatable food from the badly tasting soy bean has led to adoption of two principal methods of manufacture, namely extraction and roasting. In experiments with raw soy beans, ordinary soy flour and so-called new soy flour, the animals declined the old flour entirely, accepted soy beans very slightly and consumed only the new soy bean flour gladly. The new soy bean flour keeps well, does not become rancid and is well adapted for culinary purposes. Manifestly it is largely deprived of its fat.

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**The Biologic Relation between Chiefly Protein and Chiefly Carbohydrate Nutriment.**

*L. Berczeller, Biochem. Ztschr., Berlin, 129:320, May 3, 1922.*

Researches have shown that animals rate the closely related nutrient materials very differently and that that preference, on the whole, runs parallel with the maintenance value, as in the case of legumes. Further experiments were undertaken with individual foods such as maize and soja. These substitutes were compared with the more highly rated ones, viz. meat, milk, eggs and wheat. The experiments were carried out in the same manner as preceding ones. First, legumes were compared with each other with addition of a food containing carbohydrate. Further, maize-flour and fine wheat-flour with added protein feeding, and plant protein (soja) were compared with animal protein (milk, meat, eggs). The influence of hemoglobin on the absorption of plant protein, and, finally, the artificial alteration of maize by adding salt or sugar were studied. It was shown that the animals rated protein foods

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quite differently. In the preference for protein foods physical influences play a considerable part (state of intumescence). Rats, the same as man, value meat higher owing to its water-soluble extractives. When milk powder is added to other foods the animals consume larger amounts of the powder so that the selection of the foods takes place in accordance with a law that is likewise useful. In this experiment simple laws between duration of life and ingestion of food may be detected. Slight additions to the diet influence consumption considerably and by these the animals are misled in their selection, that is, they do not perceive the danger and reduce the duration of their lives to a twentieth by unsuitable selection. Ingestion of food is usually typically similar in the case of closely related, chemically distinguishable foods, but very different in similar but chemically and biologically different foods. By slight alterations in the individual foods the amount of total ingested food is greatly affected.

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**Studies on the Digestibility of Proteins in Vitro. III. On the Chemical Nature of the Nutritional Deficiencies of Arachin.**

*D. Breese Jones and Henry C. Waterman, J. Biol. Chem., 52: 357, June, 1922.*

The purposes of the experiments were: (1) to ascertain if incomplete digestibility of arachin could be demonstrated by experiments in vitro; (2) to determine if such an incomplete digestibility were found to exist, if it could be remedied by any means not productive of a far reaching hydrolysis; and (3) to secure, by means of a chemical study of partial degradation products of arachin, some evidence as to the identity of the amino-acids which are so combined in arachin as to be difficultly separable by proteoclastic enzymes. Regarding the first point, the results supported the tentative conclusion drawn by the authors from the preceding animal experiments. Arachin was found to be less readily digestible in vitro by pepsin and trypsin under the experimental conditions described than any biologically available proteins thus far tested by the same method. The digestibility in vitro of arachin was not appreciably increased by boiling with water at ordinary pressure, or by steaming at 15 pounds pressure. Regarding the third point, it was found that the action of hot, dilute sodium hydroxid upon arachin produced a partial cleavage derivative amounting to about one-third of the arachin from which it was prepared. This derivative contained about two-thirds of the total histidin, about one-third of the total arginin and of the total cystin, and about two-fifths of the total lysin of the original arachin. This partial cleavage product the authors found to be very difficultly digestible in vitro.

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**The Physiologic Action of Proteinogenous Amins. V. Vegetative Nervous System and Metabolism.**

*J. Abelin, Biochem. Ztschr., Berlin, 129: 1, April 19, 1922.*

Intimate relations exist between the vegetative nervous system and the thyroid gland. The thyroid exerts the typical influence on carbohydrate metabolism. After thyroid feeding the liver appears glycogen



free or glycogen deficient. Investigation of the combined effect of thyroid feeding and phlorizin injection on carbohydrate and gaseous metabolism showed that the animals exhibited greatly increased respiratory metabolism and strong glycosuria.

Increase in metabolism does not set in directly after thyroid ingestion and it dies off slowly. Certain proteinogenous amines, such as tyramin and phenylethylamin, have an analogous action on metabolism to that of the thyroid. The analogies extend to nitrogen metabolism, gaseous metabolism, glycogen mobilization and water elimination. Adler's observation that hibernating hedgehogs awake upon injection of thyroid, by which body temperature rises to its summer height and respiratory frequency is greatly increased is also familiar. The analogous action of thyroid and tyramin discovered by Wuth is of interest. In white mice increased resistance to cyanid poisoning is effected, not only by previous thyroid treatment, but likewise by tyramin injections. The attacking point of these substances is not known. Very probably the vegetatively attacking substances represent strong stimulating agents of metabolic processes but effect merely quantitative alterations of physiologically existent stimuli. Under these circumstances great importance must be assigned to the vegetative nervous system and to the agents acting upon the same in regard to the regulation and degree of metabolic processes.

Experiments were undertaken in which the analysis of the action of tyramin and phenylethylamin on metabolism were investigated exactly. Results show that not only tyramin and phenylethylamin, but also various other representatives of substances attacking the vegetative nervous system, influence metabolic processes. Adrenalin, cholin, pilocarpin and atropin are able to increase gaseous metabolism the same as tyramin and phenylethylamin and the increased metabolism is accompanied by increased urine excretion. All sympathetically or parasympathetically attacking substances here mentioned, as well as thyroid substances, affect in addition carbohydrate metabolism by inducing glycogen mobilization, hyperglycemia and glycosuria. Herein the action on carbohydrate metabolism is to be regarded as only a partial phenomenon of the general metabolic action, inasmuch as carbohydrate metabolism is intimately related to the entire metabolism of the organism. Tyramin and phenylethylamin reinforce each other in their action on metabolism and this action may be increased further by employing, simultaneously with these amines, other thyroid substances. Very small and, as such, inactive amounts of tyramin and phenylethylamin when added to otherwise also inactive amounts of thyroid substances effect strong increase of gaseous metabolism.

Such a method of application makes it possible to reduce the requisite therapeutic amounts of thyroid very considerably. It is probable that the metabolic action of the thyroid is merely an expression of the general influence on the vegetative nervous system. The present researches also support the view that the vegetative nervous system is of great importance in the regulation of the degree and nature of the entire assimilation. As in the case of many other substances that attack the vegetative nervous system, so with tyramin and phenylethylamin, the action is found to depend on dosage and manner of application.



Gaseous metabolism experiments on rats and on a thyroidectomized dog showed that peroral administration of small amounts of tyramin and phenylethylamin diminished gaseous exchange. Frequently a simultaneous distinct increase of the respiratory quotient is observed as the expression of augmented carbohydrate combustion. Adrenalin behaves the same as tyramin and phenylethylamin. Its subcutaneous injection in rats causes strongly increased gaseous exchange, but in peroral administration it diminishes carbon dioxid elimination and oxygen consumption. In larger doses tyramin and phenylethylamin produce increase of gaseous exchange also under peroral administration. Histamin was without influence on gaseous exchange and its physiologic action is altogether of a wholly different nature to that of tyramin and phenylethylamin. In hitherto conducted experiments acetylcholin reduced gaseous metabolism distinctly.

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**The Rôle of Cystin in the Dietary Properties of the Proteins of the Cow-Pea, *Vigna Sinensis*, and of the Field Pea, *Pisum Sativum*.**

*A. J. Finks, D. Breese Jones and Carl O. Johns, J. Biol. Chem., 52: 403, June, 1922.*

The authors studied the nutritive value of the proteins of the cow-pea, *Vigna sinensis*, and the field pea, *Pisum sativum*, by feeding to albino rats cow-pea meal and field pea meal, and observing the rate of growth. Only one-third to two-thirds of the normal rate of growth of the rats was obtained on a diet in which 70% cow-pea meal, equivalent to 16.5% protein, furnished the sole source of protein. Field pea meal, fed at the same protein level, enabled rats to grow at a practically normal rate without the addition of cystin or cooking. The proteins of the field pea and those of the cooked cow-pea plus cystin were equally efficient in promoting growth at a practically normal rate, while the proteins of the cow-pea raw plus cystin, or cooked without cystin, were less than half as well utilized as those of the field pea.

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**The Relation Between the Endogenous Catabolism and the Nonprotein Constituents of the Tissues.**

*H. H. Mitchell, W. B. Nevens and F. E. Kendall, J. Biol. Chem., 52: 417, June, 1922.*

The authors believing the endogenous catabolism of nitrogenous compounds sufficiently important, theoretically and practically, to justify experimental investigation, studied the effect of feeding a low protein diet of starch and cream on the concentration of nonprotein nitrogenous compounds in the tissues of rats, hoping to throw more light on this obscure type of catabolism.

Twelve male rats, weighing from 200 to 300 gm. each, were placed upon a ration of milk and dog biscuit. Six of them were taken off this ration, killed and analyzed after being fasted for 19-26 hours. The remaining 6 were changed to a synthetic ration containing minimal amounts of nitrogen. Of these, 1 was killed after being kept 24 hours on the experimental diet, 1 was killed after 48 hours, 2 after 11 days,

and 2 after 22 days. The ration contained 76% starch, 10% butter fat, 8% sucrose, and 3% each of salts (Osborne and Mendel's mixture) and agar; also a small amount of Osborne and Wakeman's Fraction II from yeast as a source of vitamin B. On analysis, this ration was found to contain 0.82 mg. of nitrogen per gram. The rats were killed with ether, the intestinal tract cleansed with distilled water, and the entire carcass then passed twice through a meat-grinder. The ground material was immediately extracted with boiling water slightly acidified with acetic acid. When the first portion of water was added the mixture was quickly brought to boiling to prevent enzymic changes. Each carcass was extracted 8 times with 5 times its weight of boiling nitrogen-free water, and was digested on the steam-bath for 15-30 minutes after each addition of water. The extracts were filtered through funnels containing a loose plug of glass-wool, covered by layers of cheese cloth. The filtrates were collected and made up to a definite volume, and aliquots analyzed for total nonprotein nitrogen, ammonia, amino-nitrogen, urea, and creatin. Occasionally the total soluble nitrogen was also determined.

For the 2 rats kept for 11 days on the nitrogen-free ration, and for the 2 kept for 22 days on this ration, daily collection of urine and feces were made and analyzed for nitrogen, to determine how soon the rat reached its minimum endogenous catabolism of nitrogen and how constantly the minimum was maintained from day to day. The tabulated results show that on a nitrogen-free diet the rat very quickly reaches a minimum nitrogen excretion, which then very slowly decreases as the body weight decreases. The authors have also compiled and tabulated additional data showing the nonprotein nitrogenous constituents of the tissues of rats in normal nutritive condition, and when the nitrogenous catabolism has been reduced to the endogenous level.

To determine the effect of the type of nitrogenous catabolism upon the total sulphur and total nitrogen of the tissues, and the nonprotein sulphur and nitrogen, 7 rats were observed. Of these 4 were taken from a normal ration, fasted for about 20 hours (1 was not fasted) and then killed with ether and prepared for analysis. Three of the rats were placed upon the same nonprotein ration used in the preceding experiment, except for the salt mixture, in which phosphoric acid was substituted for sulphuric acid. After subsisting for 10 days on this ration, the rats were killed and analysed. The authors have tabulated the total and nonprotein nitrogen and sulphur of the tissues of rats in normal nutritive condition, and in those in which the nitrogenous catabolism had been reduced to the endogenous level. No effect of the 10 days' subsistence on a nitrogen-free and sulphur-free ration can be observed in any of the values determined. The authors think the approximate constancy of the concentration of the total nonprotein nitrogen and sulphur and of the amino-nitrogen of the tissues, regardless of the type or the intensity of the catabolic processes resulting in nitrogenous or sulphur-containing end-products, would seem to be a matter of significance in formulating a theory of endogenous catabolism. They believe that the free amino-acids of the tissues are not functioning as reserve material, nor merely as intermediary steps in the synthesis and disintegration of protein, but that they are performing some distinct and important function in the life of the tissues, since such an effective mechanism

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exists for maintaining their concentration constant. The data obtained in this investigation also indicate that the total nonprotein nitrogen and sulphur are not definitely affected by the type or intensity of the protein metabolism.

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**Experiments in Glucose Permeability of the Liver.**

*E. Geiger and O. Loewi, Klin. Wchnschr., Berlin, 1:1210, June 10, 1922.*

On perfusion of the isolated frog's liver with Ringer's solution containing adrenalin, the giving off of glucose is inhibited by the rise in calcium content of the Ringer's solution, because the calcium changes the permeability. The authors made experiments with a view to determining whether the entrance of glucose into the liver is also inhibited. Soap in a concentration of 1:50,000 to 1:100,000 added to the glucose-containing perfusion fluid of the frog's heart, inhibited the taking up of glucose. In comparing the glucose intake from the serum of normal individuals with that from the serum of diabetics it was found that not a trace was taken up from the latter, but that from the former 6 to 11 mg. was taken up in  $\frac{1}{2}$  hour. It seems therefore that a substance is contained in the blood of diabetics, which inhibits the taking of glucose into the liver in the same way that soap does.

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**The Action of Phlorizin on Blood Sugar in Diffuse Bilateral Hematogenous Kidney Diseases. A Study of the Phlorizin Action.**

*Stefan Hetényi, Biochem. Ztschr., Berlin, 129:183, April 19, 1922.*

That phlorizin produces glycosuria has been known since Merings' experiments in 1885. As phlorizin glycosuria proceeds without hyperglycemia and the blood-sugar level is, if anything, reduced after a phlorizin dose, its attacking point has been shifted to the kidneys. Experiments were undertaken relating to the fluctuating of blood sugar following phlorizin injection in diffuse bilateral hematogenous kidney diseases. The experimental tables showed that the action of phlorizin is not confined to the kidneys. Under normal conditions, however, its action in inducing glycosuria is so pronounced that it entirely conceals the sugar mobilization. If the renal action diminishes or is absent entirely, for instance in certain stages of renal diseases, sugar mobilization appears in the foreground resulting in the rise of the blood-sugar level.

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**The Threshold of Ketogenesis.**

*Russell M. Wilder and Malcolm D. Winter, J. Biol. Chem., 52:393, June, 1922.*

This report is concerned with the composition of metabolizing food mixtures in 16 patients, of whom 3 were epileptics but were otherwise normal, apparently; 13 had diabetes, and of these 2 suffered from mild, acute infections. None of the epileptic patients had convulsions and the diabetic patients were without glycosuria at the time of the investigation. On the day before and on the day of the test the patients re-

mained in bed. During this period each received a constant diet consisting of rice, soy bean bread enriched with fat, butter and cream. Its composition was calculated from the Atwater-Bryant tables. The daily food allowance did not exceed in caloric value the energy needs of the patient and the protein quota was less than 1 gm. for each kilo of body weight. Precautions were taken to secure accurate collections of urine. Daily determinations of urinary nitrogen were made by the Kjeldahl method. Van Slyke's methods were followed for acetone bodies of the urine and blood and for the carbon-dioxid combining power of the plasma. The basal respiratory metabolism and respiratory quotients were secured by the gasometer method as described by Boothby and Sandiford.

The calculations of metabolizing mixtures and the ratios of ketogenic molecules to glucose molecules in these mixtures were based on these assumptions: (1) The total energy exchange, or total metabolism, is accurately represented by the basal calories for 24 hours plus 10% for the specific dynamic action of food and 10% for movements. This assumption is justified if the patient is confined to bed during the test day and for one or more preceding days, as was the case in these experiments. (2) All glucose derived from the food (carbohydrate, protein, and fat) is burned. This assumption is justified, provided the subject has received relatively little carbohydrate and protein for several days preceding the test, and provided the diet does not exceed the energy and nitrogen requirements of the subject, as was the case in these experiments. (3) No carbohydrate from endogenous sources (glycogen) is burned. This assumption is precarious, but it is presumed that the glycogen stores of patients who are on a régime very low in carbohydrate are retained tenaciously. (4) The nitrogen in grams in a 24 hour specimen of urine multiplied by 26.51 is the number of calories from the protein metabolized.

Under the conditions of these experiments, provided these assumptions are tenable, the ratio between the ketogenic and the glucose molecules at which a clinically significant ketosis appears has a value of at least 2:1. A ratio of this value implies that every molecule of glucose is ketolytic for 2 molecules of aceto-acetic acid. The existence of infection, was found to lower the ketogenic threshold so that significant ketogenesis may occur with lower ratios. It is advisable in planning diets for diabetic patients to allow only such food mixtures as will avoid the 2:1 ratio by a safe margin.

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## **Researches on the Participation of Lipoids in the Metabolism of the Plant-Cell. II.**

*Friedrich Boas, Biochem. Ztschr., Berlin, 129: 144, April 19, 1922.*

By altering the colloidal state of the cellular lipid membrane saponin bodies may effect a considerable increase in permeability. That increase may be so intense as to cause the death of the cell. The hitherto investigated saponins may be arranged in the order of their activity as follows: cyclamin, digitonin, smilacin, saponin Merck, quillaia-saponin and guaia-saponin. Experiments were undertaken regarding solanin and the action of bile acids and their salts. Of

the latter were employed: sodium cholate, sodium glycocholate, sodium taurocholate and sodium cholate prepared from crystalline cholic acid. From the experiments it appears that the saponin bodies with altered lipoids, the same as the biliary salts, promote fermentation by yeast very considerably by increasing the permeability. Thereby the 2 classes of fermentation activators are enabled to penetrate into the interior of the cell by reason of their fairly high capillary activity. In other respects, however, their action on the cell appears to be slight as only the specially highly active saponin bodies such as digitonin, smilacin, and cyclamin injure the cell considerably, like the biliary salts when the latter act in appreciable concentration on the same. The chief attacking point of these lipoid-loosening agents remains, the same as before, the cell's lipid content.

The action of the saponin bodies and of the similar bile salts differs sharply from that of narcotics and alkaloids in so far as they produce, in combination with neutral salts, extremely severe injury to the cell, usually in a short time. The injury is due to alteration of the cell's colloidal structure. The lipoids afford a certain amount of protection against rapid penetration of the cell.

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**Studies on Alkaligenesis in Tissues. II. Ammonia Production in Muscle during Contraction.**

*Olive Pearl Lee and Shiro Tashiro, Am. J. Physiol., 61:244, July 1, 1922.*

The authors undertook this investigation to determine if ammonia is produced during muscular activity. To eliminate as far as possible physiologic variations of different animals, the authors compared the 2 gastrocnemius muscles of the same frog, only one of which received break induction shocks, the other not being stimulated at all. The amount of ammonia given off by resting and contracting gastrocnemius muscle of the frog, *Rana pipiens*, was determined by the authors and recorded. Such tabulated data show that a resting gastrocnemius muscle of the frog gives off  $3.83 \times 10^{-7}$  gm. ammonia, calculated on the basis of 1 gm. of the tissue and 15 min. respiration. During 360 contractions the authors found it gives off  $7.56 \times 10^{-7}$  gm. ammonia. One gm. muscle, therefore, produces approximately  $1 \times 10^{-9}$  gm. more ammonia during a single contraction. Tetanized and injured muscle do not give off any ammonia, it was observed. This is probably due to simultaneous production of a nonvolatile acid.

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**Formation and Distribution of Phosphates in Muscle.**

*L. B. Winter and W. Smith, J. Physiol., London, 56:227, May 16, 1922.*

The authors' primary object was to compare the phosphate content of normal resting muscle with that of muscle in rigor. The test which is used to detect inorganic phosphate in tissues is the yellow precipitate of ammonium phosphomolybdate which is formed when ammonium molybdate in the presence of nitric acid is added to a phosphate solution.



This test is not satisfactory, so the authors used a 3% solution of potassium ferrocyanid which produces a blue compound. When added to ammonium molybdate in absence of acid no change of color occurs, but in the presence of nitric acid a dark red color is produced. This makes no difficulty in the preparations for if carefully washed no red color appears. After some experimenting the authors finally made up as follows 2 standard solutions: (1) ammonium molybdate 13 gm. per 100 c.c. dissolved in distilled water by the aid of heat; and (2) concentrated nitric acid to which an equal volume of distilled water was added. The solution finally adopted was made by taking 10 c.c. of solution 1 and adding to it 0.4 c.c. of solution 2. The mixture was well shaken and the precipitate allowed to settle; the clear fluid was then pipetted off and used. Comparison of resting muscle and rigor muscle in the leg muscles of the cockroach (*Periplaneta americana*) as regards phosphate content was then made. It was found that the amount of uncombined phosphate in striated muscle is increased in rigor. No appreciable amount is set free in unstriated muscle on dying.

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**Metabolism in Vitamin-Free Nutrition.**

*M. Tsuji, Biochem. Ztschr., Berlin, 129: 194, April 19, 1922.*

Owing to the small amounts in which they are absorbed vitamins cannot yield energy but merely act as energy conveyors. For energy conveyance either the circumstance that the vitamin is an integral component of cellular structure or that it acts like inorganic catalyzers may be involved. A certain analogy may therefore exist between the action of salt and vitamins on metabolism of the organic substance in the body. In that case the metabolic disturbances in the organic substance that follow either salt deficiency or vitamin deficiency would be identical in this or that direction. Deficiency in both factors would be followed by an increase of certain metabolic disturbances that is produced also by the deficiency of only one or other of these factors. Experiments on metabolism in the dog were therefore undertaken in which the animal received a salt-deficient in addition to the vitamin-free diet. Regarding the effect of a vitamin-free and saliferous diet, it is known to cause loss of weight. Observations touching the influence of a salt-deficient but vitamin-rich nutrition indicate that an increase of sodium chlorid in the food conserves nitrogen while sodium chlorid deficiency promotes the decomposition of nitrogen in the body.

The experiments showed that the vitamin-free fed dog behaves like the animal in a state of intense undernutrition as described admirably by Loevi in his work on Undernutrition. An analogy also exists to certain affections of the thyroid. In common with hyperthyroidism the metabolism of albumin, fat and carbohydrates is increased and gaseous exchange is reduced in the fasting state. Further, the metabolic disturbance in avitaminose recalls the decomposition of albumin in fever and the toxic albumin disintegration in certain cases of carcinomatosis, in infectious diseases and anemias and in phosphorus poisoning. Avitaminous metabolic disturbance differs from a state of hunger in that, in hunger the nutrient material is absent, while though present in avitaminose, it is incapable of being utilized in the proper physiologic



manner. The cell starves although nutrient substances traverse it in liberal amounts.

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**The Relation of Nutrition to Tooth Development and Tooth Preservation.**

*E. V. McCollum, Nina Simmonds, Ethel M. Kinney and Clarence J. Grieves, Bull. Johns Hopkins Hosp., 33:202, June, 1922.*

This extensive report gives the results of a research upon hundreds of rats fed upon 57 different diets, so composed as to be defective in necessary elements. It was found that definite lesions of the teeth and jaws, such as dental caries, dental fracture, gingivitis, pyorrhea, dental abscess, and alveolar bone disease, were all produced in animals fed on the defective diets, though practically absent from the controls. It appears that no specific deficiency underlies these diseases, but any slight variation from an adequate diet apparently favors their production. The percentage of oral defects was highest in rats fed on a diet deficient in protein, calcium and fat-soluble A. Next came those fed on a diet deficient solely in calcium, and third were those lacking both calcium and fat-soluble A. Lesser percentages of oral disease occurred with diets low in calcium and high in fat-soluble A, those low in protein and fat-soluble A or in fat-soluble A alone. Diets high in calcium and low in fat-soluble A, high both in calcium and cod-liver oil, and those low in calcium and in cod-liver oil, cause the least percentage of dental disease. The antineuritic and antiscorbutic vitamins were not tested in these experiments. The paper contains extensive tables and numerous illustrations.

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**The Nutritional Requirements of Baby Chicks. II. Further Study of Leg Weakness in Chickens.**

*E. B. Hart, J. G. Halpin and H. Steenbock, J. Biol. Chem., 52:379, June, 1922.*

In the experiments a hatch of 57 pure-bred Rhode Island Red chicks was divided into 3 groups of 19 each. They were confined indoors and to limited runs with shavings as a litter. Group 1 received as a mash, a mixture of 97 parts of white corn, 2 parts of calcium carbonate, 1 part of sodium chlorid; skimmed milk was allowed ad libitum. Group 2 received the same ration as Group 1, to which were added 50 gm. cod-liver oil per kilo of grain-salt; the cod-liver oil was mixed intimately with the ration. Group 3 served only as a control and received a more complex diet, consisting of a mash of 33 parts of bran, 32 parts of yellow corn, 32 parts of middlings, 1 part of charcoal, and 2 parts of fish scraps; whole milk was allowed ad libitum; a scratch mixture of 50 parts of yellow corn, 25 parts of wheat, and 25 parts of oats was also allowed. In addition to the calcium carbonate included in the rations of Groups 1 and 2, limestone grits were allowed all the birds. No water was given, it being derived wholly from the skimmed milk.

The tabulated results show that with 1 exception all of the animals of Group 1 died within 6 weeks after the initiation of the experiments. Group 2, receiving the cod-liver oil in addition to the basal ration, made with 2 exceptions uniform and rapid growth. The 6 birds from

Group 3 which had received a complex diet and were transferred at weights of 200 gm. or more to the low fat-soluble vitamin ration given Group 1, grew well for 3-5 weeks after the transfer and then began to fail. The results indicate to the authors that this species requires a liberal supply of the vitamins of cod-liver oil during its most active period of growth, but that the water-soluble and antiscorbutic vitamin requirement can be met by the amounts contained in a cereal grain and skimmed milk. When the cod-liver oil was omitted from the ration the animals died in 4-6 weeks. The inorganic phosphorous content of the blood of the chicks in this group was low as compared with those receiving cod-liver oil.

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**Studies on Experimental Rickets. XX. The Effects of Strontium Administration on the Histologic Structure of the Growing Bones.**

*P. G. Shipley, E. A. Park, E. V. McCollum, Nina Simmonds and Ethel May Kinney, Bull. Johns Hopkins Hosp., 33:216, June, 1922.*

Young rats were fed on a diet containing all the elements necessary to growth, except that calcium was very low. On this diet growth did not occur, and lesions of the bones resulted which showed a picture like that called by Schmorl "pseudorachitic osteoporosis"; it is apparently a condition on the border line between rickets and osteosclerosis. In order to test the value of strontium as a substitute for calcium, strontium chlorid to the extent of 2.2% of the diet was added. Rats given this diet grew to 2 or 3 times their initial weight (i. e. partial growth), but developed a condition of marked deformity of the skeleton, resembling rickets, accompanied by paralysis of the extremities. Histologically, the bones showed persistence of cartilage and increased formation of osteoid tissue—an exaggerated form of rickets. Cod-liver oil does not compensate for this faulty diet as it does for a disproportion between calcium and phosphorus in the diets used to produce ordinary experimental rickets. Lesions previously described by Lehnert (1910) as produced by strontium in the diet, are shown to have been due not to the strontium but to a disproportionately high phosphorus content.

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**Studies on Experimental Rickets. XXI. An Experimental Demonstration of the Existence of a Vitamin which Promotes Calcium Deposition.**

*E. V. McCollum, Nina Simmonds, J. Ernestine Becker and P. G. Shipley, Bull. Johns Hopkins Hosp., 33:229, June, 1922.*

These authors have previously published evidence which has led them to suppose that the protection against rickets afforded by cod-liver oil is not due to the fat-soluble vitamin A. A more exact proof is now given by making use of the fact which Gowland Hopkins has discovered, that fat-soluble A is readily destroyed by oxidation. The authors have oxidized cod-liver oil by blowing air through it for 12-20 hours at 100° C. Oil thus treated lacks fat-soluble A, as shown by the fact that it fails to cure xerophthalmia, but it still possesses its curative properties for rickets unchanged. The existence of a fourth vita-

min, exerting its effects upon calcium deposition in growing bones, is thus as firmly established as that of the three hitherto recognized vitamins.

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**The Potency of Commercial Vitamin Preparations.**

*E. V. McCollum and Nina Simmonds, J. A. M. A., 78: 1953, June 24, 1922.*

Owing to the rapid growth of the traffic in commercial vitamins, the authors thought it important to examine some of the preparations for their potency as sources of the most stable of these, the water soluble B, or vitamin B, the antineuritic substances. Six of the products for vitamin B which have been more or less widely advertised were tested. The claims set forth on the labels of the medicinal values of these preparations are extravagant and misleading. They do not contain the vitamin B in concentrated form as they are represented to do. The drug store is not the place to secure vitamins. Milk and leafy vegetables are of outstanding importance in that they are so constituted as to make good the deficiencies of the white bread, meat, potato and sugar type of diet. Reduced to its simplest terms, the most important dietary reforms which the authors can introduce are: salads should be eaten twice each day. This will insure the regular consumption of more raw fruit and vegetables. Each day a liberal helping should be taken of some food classed as pot-herbs, and a quart of milk or its equivalent in the form of manufactured dairy products should be taken. The remainder of the diet may be selected entirely on the basis of its appeal to the sense of taste.

Tests were made on rats fed on 3 diets: (1) a deficient diet; (2) a diet supplemented by vitamin tablets; and (3) a diet supplemented by wheat germ. It was demonstrated that young rats can be given as much as 80% of wheat germ (fat free) properly supplemented with respect to calcium and fat-soluble A, without interference in any way with their rapid growth in experiments covering several weeks. This shows that 20 times the dosage of water-soluble B that just suffices to induce normal growth does not disturb the health of young rats in such intervals of time as are covered by the tests.

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**A Physiologic Test for the Activity of Vitamin Preparations.**

*Atherton Seidell, Pub. Health Rep. (U. S. P. H. S.), 37: 1519, June 23, 1922.*

Any improvement in the accuracy and rapidity of the tests for guiding the fractionation of vitamins is a matter of importance. Formerly the curative effect on fowls, brought to the polyneuritic state by a vitamin deficient diet, was used to determine the presence of vitamin in the sample. Now pigeons are fed on polished rice as the most satisfactory vitamin-free diet and in addition are given vitamin activated fuller's earth in doses just sufficient to prevent an appreciable loss in weight, so that they reach a state approaching vitamin equilibrium. Although birds on this diet do not reproduce, they show no perceptible

signs of malnutrition even after long periods and are constantly in a state in which the withdrawal of vitamin is promptly manifest. An attempt to improve the quality of the diet might diminish its accuracy. The samples to be tested for their vitamin content replace the doses of "activated solid," and weight changes in the pigeons can be detected for quantities of sample varying by 0.1-0.2 gm. Positive results can usually be obtained within 2 weeks and the birds can then be made ready for another test within 10 days. There is necessity for caution against giving doses in excess of the amount required for maintenance of weight so that for each sample some of the pigeons should receive slightly deficient doses.

Experiments have shown that a sample of the new "activated solid" which contains 1.5% nitrogen protects the pigeons in doses of 0.1 gm. given on alternate days—1.5 mg. on the nitrogen basis. By barium hydroxid extraction and readsorption it was found that not more than one-third of the nitrogen in the activated solid is present in vitamin combination and further experiments determined that the deficiency of the rice diet was replaced by doses of 0.04 mg. If it is assumed that the vitamin-free base contains 20% nitrogen, 0.04 mg. active nitrogen corresponds to 0.2 mg. uncombined vitamin base, and with this figure in mind it will not be necessary to undertake identification tests upon fractions which, in daily doses greater than 0.25 mg. do not protect pigeons from loss in weight on polished rice.

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**Fish-Liver Oils and Other Highly Potent Sources of Vitamin A.**

*S. S. Zilva and J. C. Drummond, Lancet, London, 202: 1243, June 24, 1922.*

The livers of cod, coal-fish, haddock and others contain large stores of vitamin A. This study was undertaken in order to determine the best methods of preparing the oils and to find why the liver should contain these large stores. The livers are treated either by the steam jacket or by direct steam, and the oils obtained are then refined. There is very little destruction of the vitamin, but the direct steam method is slightly more deleterious. There is considerable variation in the potency of the various oils, and this must be explained, not by the method of preparation, but by some physiologic factor such as the food or the sexual condition. Cod roe is a very rich source of vitamin A. The highest activity was found in coal-fish livers and the lowest in the haddock. High vitamin content was found in cod-liver oils of British and Newfoundland origin, as well as in the Norwegian oils. Other workers have found that a small amount of butter (3%) has a beneficial effect on bone formation in rats whose calcium content was half the requirement, but that 20% butter failed when the calcium content was one-fifteenth of the optimal requirement. Much better deposition of bone was obtained by the use of 1% cod-liver oil. The authors found that cod-liver oil contains more than 200 times as much fat-soluble vitamin as butter, and therefore the equivalent amount in butter could not possibly be administered.

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**The Influence of Hydrogen Sulphid upon Respiration.**

*Howard W. Haggard and Yandell Henderson, Am. J. Physiol., 61:289, July 1, 1922.*

One of the authors has shown that hydrogen sulphid introduced into the blood stream, either through the inhalation of this gas or by the hydrolysis of sodium sulphid in the blood, is rapidly oxidized to nontoxic compounds. The explanation of the capacity of the body to withstand small amounts of hydrogen sulphid, while slightly more, is markedly toxic, evidently depends upon this capacity of the blood to oxidize and thus detoxicate hydrogen sulphid up to a certain limit. It was also shown that no combination of hydrogen sulphid is effected with the hemoglobin, except under diseased conditions of special etiology. The effects of hydrogen sulphid are therefore not in the nature of an asphyxia, except to the very slight extent to which the blood is depleted of oxygen in the oxidation of the hydrogen sulphid. The physiologic effects of this gas are exercised through the gas in solution in the plasma of the blood. The respiratory response to sulphid must then be a result of the action of the hydrogen sulphid dissolved in the blood upon some mechanism controlling respiration. The authors suggest 3 possibilities: (1) the action may be directly and specifically upon the respiratory center in the medulla; (2) it may alter the H-ion equilibrium of the blood; or (3) it may stimulate some respiratory mechanism other than the center, for example the vagal endings in the lungs. For the investigation of these 3 possibilities the action of sulphid on dogs was observed after section of the vagi. The authors found that sodium sulphid (2 mg. per kilo) when injected intravenously liberates hydrogen sulphid in the blood and induces hyperpnea, followed by apnea vera. This does not occur after section of the vagi. Apparently therefore the stimulating action of sulphid upon respiration is chiefly due to irritation of the afferent endings of the pulmonary vagi. Upon the respiratory center small amounts of sulphid are generally without perceptible effect. Larger amounts paralyze respiration.

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**The Measurement of Neuromuscular Electric Excitability in Man.**

*A. Strohl, Arch. d'électric. méd., Bordeaux, 30:129, May, 1922.*

Weiss stated the relations of time and intensity as follows: For bringing a nerve or muscle to the stimulus threshold, a certain constant quantity of electricity must be supplemented by a quantity variable and proportional to the duration of the passage of the discharge. The excitability, or chronaxia, coefficient expresses numerically the functional condition of nerve and muscle. For the various human muscles, it ranges from 0.0001 to 0.001 second, increasing in degeneration, where it may amount to several hundredths second. It is thus a very delicate criterion in diagnosis.

Author prefers continuous currents of very brief and variable duration. A satisfactory apparatus has been constructed by Gaiffe, Gallot and Pilon. It is called the egersimeter. A heavy mass, falling down a column, operates 2 switches in passing, the current flowing through the body during the passage between the switches. The distance between the switches may be varied and curves are provided for reading. Cur-



rents varying from a fraction of 0.001, to 0.01 second may be utilized. Even with current of long duration, excitation terminates, in rapid muscles of man or frog, in a few thousandths second. It is important to know the resistance of the subject during the first few instants following closure of the circuit. For currents between 1 and 10 milli-amperes, the resistance does not change appreciably. When the voltage is doubled, the resistance may fall to 0.3, its initial value, almost instantaneously.

The resistance rises rapidly during the first ten-thousandths second after closing the circuit. This increase is very important. In 0.001 second, with a current of 20 volts, a resistance of 3700 may rise to 50,000 ohms. The resistance slowly declines after the initial rise, the speed of the decline becoming less as the current continues to flow. The higher the voltage, the nearer the maximum resistance to the closure of the circuit. With 40 volts, the maximum resistance of the body is not more than 7000 ohms and with 80 volts it does not exceed 3000 ohms. The brief increase in resistance is due to a polarization current flowing against the current introduced. The polarization current originates in the tissues, rises very quickly to a maximum, and then declines. For very brief periods (e. g. 0.0002 second) the polarization current equalled 10.5 volts. After 7 seconds, it fell to 0.3 to 0.5 volts. The voltage is the most important factor in stimulation. The voltage should be kept high by varying the resistance in the circuit according to the excitability of the muscle or nerve.

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**The Possible Existence in the Cortex of an Anovesical Center.**

*E. D. Paulian and P. Topa, Bull. et mém. Soc. méd. d. hôp. de Paris, 38:915, June 15, 1922.*

The authors describe a case occurring in a man of 32, who had undergone a cranial operation 26 years before for an injury. Some 5 years ago symptoms appeared consisting of continual urinary incontinence, impaired memory and sudden attacks of unconsciousness, without convulsions, but accompanied by cries. Obstinate constipation also developed. At operation, the old cicatrix was removed. Beneath it a callus on the inner table of the bone, adherent to the dura, was removed, the dura freed and the opening covered with a celluloid plate. By the fourth day, the daily incontinence had nearly ceased, the nocturnal remaining; by the seventh day, all incontinence ceased and cure was complete a month after the operation. The authors located the irritation in front of the paracentral lobule, on the crest of the first right frontal lobe, on the right side. Pressure at this point may have affected an anovesical center existing in that region. A real effect seems to have followed the operation and the cure does not appear referable to suggestion.

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**The "All-or-None" Principle Applied to Mammalian Nerves and Reflex Arcs.**

*J. M. D. Olmsted and W. P. Warner, Am. J. Physiol., 61:228, July 1, 1922.*

After studying Adrian's experiments, which are considered proof  
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that conduction in the frog's motor nerve follows the all-or-none law, the authors were convinced that the same method could be applied to a study of conduction in mammalian nerves and to a certain degree to conduction over reflex arcs. Accordingly experiments were performed on decerebrate cats prepared according to Sherrington's method. In nearly all the experiments the muscle used was the tibialis anticus and the contractions were recorded isotonicly. The motor nerve for this muscle is the peroneal; and the sensory nerve for reflex stimulation, the popliteal. In their studies the authors observed, in connection with the motor nerve: (1) relation of strength of stimulus to its previous history; and (2) maximal and minimal stimuli during narcotization. The authors found that in the mammalian motor nerve fibers, like the frog's motor nerve fibers, there is an all-or-none relation between the strength of stimulus and the size of the propagated disturbance which follows it. Similarly, the sensory nerves of the cat, and reflex arcs as well, conduct nervous impulses according to the all-or-none principle, provided conditions are kept constant, especially the state of excitability in the central nervous system.

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**The Localization of Excretion in the Uriniferous Tubule.**

*J. M. O'Connor and E. J. Conway, J. Physiol., London, 56: 190, May 16, 1922.*

The theories of urinary secretion set forth by Ludwig and Bowman differ fundamentally in this, that according to the Ludwig theory the entire excreta of the kidney must pass into the tubule through the glomerulus, whereas according to the other class of theories particular substances can join the urine in its course through the convoluted tubes. If one applies the Ludwig view to any particular substance one would expect that on an injection of that substance into the blood stream, the urine emerging from the lower end of the ureter would show an increased concentration only when the previous contents of the ureter, pelvis, collecting tubes and uriniferous tubules had been expelled. If on the other hand the substance reached the urine even in part through the second convoluted tubule an increased concentration would show itself when the contents of the system from the junctional tubule downward had been expelled.

O'Connor and Conway obtained an approximation to the value of these quantities in the rabbit. Using the figures so obtained merely as an example one would expect, that if the urine coming from the lower end of the ureter were collected in drops of 20 c. mm. a substance excreted by the second convoluted tubule would appear, or appear in increased quantity, in the third or fourth drop after the injected substance reached the kidney, but a substance excreted by the glomerulus only would not show itself until the eighth or ninth drop. The time the injected material reaches the kidney can be taken as 7 seconds after the injection. As the convoluted tubules lie close around the glomerulus to which they belong the arrival of the injection at the glomerulus and at the convoluted tubule may be taken as simultaneous. The authors applied the plan to 3 substances, chlorids, uric acid, and iodids, performing the experiments on anesthetized rabbits. The experiments on the intravenous injection of sodium chlorid sug-

gested that while sometimes excreted by the tubule it is in other cases excreted by the glomerulus alone. The author's experiments with uric acid showed that it was excreted by the second convoluted tubule. Those with injections of sodium iodid showed that iodid is generally excreted at a higher level, probably by the glomerulus.

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**Glucose Absorption in the Renal Tubules of the Frog.**

*G. A. Clark, J. Physiol., London, 56: 201, May 16, 1922.*

Author's experiments were undertaken to ascertain if the renal tubule played any part in preventing the blood-sugar from passing into the urine. The method of perfusion employed was that described by Bainbridge, Collins and Menzies. The perfusing fluid, in which varying amounts of sugar were dissolved, had the following composition: NaCl, .5%; KCl, .01%; CaCl, .02%; NaHCO<sub>3</sub>, .285%. Winter frogs which had been kept in a semidark tank and whose blood-sugar content was found to vary between .020% and .027% were used. Experiments were first performed to determine the renal threshold for glucose. In these, both aorta and renal-portal veins were perfused with fluid having the same concentration of sugar. It was found that when the perfusing fluid contained .052% glucose or less, no sugar could be detected in the urine. Thus a threshold of .052% would amply provide against escape of glucose into the urine under normal conditions. When the perfusing fluid had a glucose content above the threshold but less than .23%, the percentage of sugar in the urine was always less than that in the perfusing fluid by .05% to .06%. With concentrations above .23% the kidney allows the whole of the glucose to escape in the urine.

To ascertain the effect of this increased concentration of glucose on the tubules alone, author took advantage of, and verified, the established fact that if the renal-portal vein be perfused with Ringer's fluid so as to contain as much as .5% Ringer's fluid at twice the venous pressure, no sugar can be detected in the urine. Under these conditions, the venous perfusion does not reach the glomerulus and no sugar passes into the urine through the tubule epithelium. Author found that with a venous perfusion containing .4% or .5% glucose, while the arterial contained less than .1%, the rates of flow of the two were about equal, and in many cases the arterial rate was greater than the venous; the increased sugar content appeared to retard the flow. Thus the concentration of glucose in the fluid in the tubule capillaries would depend on the relative amounts of the 2 perfusions mingling there; this concentration can be determined by estimating the glucose in the mixed perfusate flowing from the vena cava. The renal arteries were perfused with a fluid containing less than .1% glucose, while the venous perfusion contained .4% or .5%.

The tabulated results show that when the mixed perfusate contained .21% glucose or more, the urine had the same percentage of sugar as the arterial perfusing fluid, that is, the kidney was completely permeable to the sugar in the arterial perfusion. That complete permeability was obtained when the mixed perfusate contained .21% glucose, while in the previous experiments .23% was necessary, the author attributes to the fact that the presence of the testes and fat bodies increased the proportion of arterial perfusion in the mixed perfusate.

That the effect of the increased sugar percentage is not on the glomerular membrane is obvious, because the renal-portal perfusion does not reach the glomerulus. Moreover, the sugar in the urine cannot be derived from that in the venous perfusing fluid because it has been shown by other workers that no sugar passes through the tubule epithelium; the fact that in each case the glucose content of the urine is identical, within the range of experimental error, with that of the arterial perfusing fluid, is also against this explanation. The only possible conclusion is that normally glucose is filtered through the glomerular membrane, which is completely permeable to glucose even when the latter is present in the blood below the threshold value. The epithelium of the renal tubules has the power to absorb glucose from the glomerular filtrate up to the normal threshold value. This absorption is possible until the capillaries surrounding the tubules contain glucose at a concentration of 9 or 10 times that normally present in the blood.

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**Salt and Water Elimination in Man.**

*M. M. Baird and J. B. S. Haldane, J. Physiol., London, 56:259, May 16, 1922.*

The authors served as subjects for these experiments which were undertaken to investigate the retention of water which it was found occurs when it is taken after a strong salt solution. The salt ingested was either 38 gm. NaCl, 29.25 gm. NaCl plus 12.6 gm. NaHCO<sub>3</sub>, which contains the same number of molecules, or a mixture in which K, Ca and Mg were present in about the quantities found in plasma. Each of these doses represents the salts of about 4.5 litres plasma or 4.1 colloid-free plasma. All 3 caused much the same flow of urine. In the experiments, the chlorid-bicarbonate mixture was drunk in 500 c.c. water, beginning about 2 hours after breakfast. An amount of water varying from 0 to 2.5 litres was then drunk, beginning 3¼ hours after the first salt solution. So long as the total amount of water drunk was less than 3 litres, the rate of water excretion was entirely independent of the amount taken. When 3 litres in all were drunk there was in one case a second maximum in the water excretion rate; in the other this did not occur, though a further half litre of water caused a large diuresis. The sum of the molecular concentrations of chlorid and bicarbonate rose rapidly to a steady value of about .29 nn., as previously observed by one of the authors. This value fell only if there was a secondary diuresis. The salt excretion thus ran closely parallel to the water excretion. The authors conclude that the diuresis produced by drinking hypertonic salt solutions is independent, within wide limits, of the amount of water ingested. Salts are less mobile within the body than water.

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**The Secretion of Sweat. II. The Effect of Vasoconstriction and of Adrenalin.**

*J. N. Langley and K. Uyeno, J. Physiol., London, 56:206, May 16, 1922.*

In Part I of this series it was observed that injection of Ringer's  
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fluid into the pad of a cat's foot usually caused more secretion of sweat than did injection of adrenalin, while the latter caused a more or less long lasting depression in the response of the glands to pilocarpin. The explanation of the effect of adrenalin solution appeared to be that the fluid in which the adrenalin was dissolved caused the secretion, and that the vasoconstriction produced by adrenalin itself caused the decrease in response. In this paper the authors have compared in further experiments the effect of injecting Ringer's fluid with that of injecting adrenalin, and have investigated the effect of vasoconstriction. It was first noted that all noninjurious aqueous solutions tend to stimulate slightly the sweat glands. The secretory effect of adrenalin was usually markedly less than that of Ringer's fluid. The secretory effect of the former is confined to the area in which fluid is injected. Clamping the common iliac artery and local injection of adrenalin primarily affect the secretion caused by pilocarpin in the same way. If the excitability of the glands is high, neither stops the secretion at once; if the excitability is low, either stops it in a few seconds. Similarly, if the blood supply is cut off, either by clamping the artery or by local injection of adrenalin, local injection of pilocarpin will cause secretion if the excitability is high and will not cause secretion if the excitability is low. The depressive action of adrenalin is then caused by vasoconstriction and not by direct action.

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**The Relation of Nerve Supply and Blood Flow to Sweating Produced by Pilocarpin.**

*J. H. Burn, J. Physiol., London, 56:232, May 16, 1922.*

In Burn's experiments kittens were used. In the majority of the experiments the dose of pilocarpin used was 0.5 mg. of the nitrate, which was injected subcutaneously into the loose skin of the flank. About 5 minutes later the paw under investigation was closely watched for about 10 minutes in comparison with the corresponding normal paw and the time of the first appearance and the total amount of sweat were carefully noted. Burn observed the degree of sweating after nerve degeneration (section of the sciatic nerve, section of the brachial plexus, and extirpation of the stellate ganglion) and the relation of sweating in a denervated area to the state of the circulation. The tabulated results show that degeneration of the sympathetic nerve supply is not followed by diminished response to pilocarpin of the sweat glands in the cat's foot. In fact, the sweating is often increased. Degeneration of the whole mixed nerve supply to the limb is accompanied immediately by exaggeration, but usually, after a variable longer period, by great diminution of the sweating evoked by pilocarpin. Author found that the sweating-response to pilocarpin, depressed after complete denervation, can be temporarily restored by subcutaneous injections of adrenalin, or by a period of anesthesia with ether.

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**The Evolution of the Human Races in the Light of the Hormone Theory.**

*Sir Arthur Keith, Bull. Johns Hopkins Hosp., 33:195, June, 1922.*

This paper is an abstract of Keith's second and third Herter Lectures (Sec. 1—Page 246)

tures (1921). The external features and racial characteristics of human beings are largely controlled by the hormone products of the endocrine glands. The characteristics of the existing races of mankind are so much like the variations produced by known or supposed effects of endocrine disorders upon the human frame that Keith supposes these races to have arisen through the hereditary perpetuation of the respective endocrine effects. Thus the gorilla and Neanderthal man are examples of overaction of the pituitary growth-mechanism, like acromegaly in man. Skin and hair characteristics are dependent upon the adrenal-thyroid-pituitary complex. Mongolism, cretinism, and achondroplasia are forms of thyroid disorder which are simulated to some extent by the Mongolian race. The Mongolian race among men, the orang-utan among apes, and the bulldog among canines, all represent a thyroid deficiency perpetuated by heredity. The hairless face of the negro and mongolian are supposed to be due to an adrenal effect which is active in the fetus of all races, but is persistent in the adult only of certain races. In brief, the hormone systems represent automatic growth mechanisms which are hereditary and variable, and hence supply perfectly the theoretic element in inheritance for which Darwin invented his theory of pangenesis.

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**Effect of General Excitement and of Fighting on Some Ductless Glands of Male Albino Rats.**

*Toshio Uno, Am. J. Physiol., 61:203, July 1, 1922.*

In Uno's experiments male albino rats were electrically stimulated and encouraged to fight each other in a cage. Subsequently the fighting animals were etherized and the hypophysis, suprarenals and thyroid removed. Comparison was then made with nonstimulated rats (which served as controls) as regards changes in the weight of these glands, water content and action of the extracts. The results for the thyroid and the suprarenals were entirely negative, but after 3-6 hours' stimulation and fighting, the hypophysis increased in weight, but the percentage of water showed no significant change. The extracts of the test glands caused a contraction of the intestinal strip.

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**Experimental Hyperfeminism.**

*Josef Bondi and Rudolf Neurath, Wien. klin. Wchnschr., 35:526, June 8, 1922.*

The experiments were directed toward producing a hyperfeminization by the transplantation of ovaries of nonpregnant animals of the same species and as nearly as possible the same age. Emphasis is laid on the animals being of the same species and as nearly the same age as possible, because the authors think this is the best way of bringing about a summation of similar hormones. They used in each of their first 5 series of experiments a litter of rats about 5 months old, which contained 1 or 2 male individuals and 7 to 9 female ones. Two or three of these served as donors of the ovaries, and these were implanted in the other females, both ovaries being implanted in half the cases and in the others one, either in the musculature of the abdomen or the back.



Eight days after the operation the animals were placed with a sexually mature male animal. The striking fact was noted that among 27 animals only 3 became pregnant, though the males were admitted in the second week after operation.

The authors believe from their histologic studies of the transplants that the normal hormone of the ovary has a certain destructive action on the development and persistence of the transplant, in that it inhibits the maturation of the follicle and the formation of the corpus luteum and the interstitial gland. It seems probable further that as a result of the transplantation the development of the follicle was not always prevented, but that the condition of the uterus was so backward that pregnancy was difficult or impossible.

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**Feeding Experiments on Tadpoles: Prostate Gland and Other Substances.**

*J. M. Rogoff and Wm. Rosenberg, J. Pharmacol. & Exper. Ther., 19: 353, June, 1922.*

In the first series the tadpoles were fed with the prostate and control substances in 50 mg. doses every other day, and fresh liver for 1 hour on alternating days. In the second series the same amount of material was fed daily, with fresh liver offered for half the usual period every other day. Feeding was continued until most of the tadpoles showed legs or well marked leg buds. This was seen, in both series, in the tadpoles getting prostate or the other substances several days before it was manifested in those getting only fresh liver daily. At the time when the experiment was discontinued, the tadpoles receiving fresh liver only on alternating days did not yet show leg buds and were smaller than any of the others. The tadpoles receiving fresh liver every day grew more rapidly than those getting liver every other day, and the tadpoles getting the desiccated products grew more rapidly than either.

If only the tadpoles receiving fresh liver were used as controls, it would be possible to interpret the results obtained with the prostate glands as positive. But this only emphasizes the importance of making adequate controls in experiments of this nature. For it is this disturbing factor which must be eliminated in feeding experiments with thyroid substance when the product is very weak in active material, and only such results should be interpreted as positive as clearly show a more definite effect than the above-mentioned phenomena, which may be caused by many substances other than thyroid. Since thyroid retards growth while the other materials studied seem to increase growth, the difficulty is not so great as might be apparent.

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**The Effects of Prostate Substance on the Metamorphosis of the Intestine of Frog Tadpoles.**

*Robert W. Hegner, Am. J. Physiol., 61: 298, July 1, 1922.*

The author's experiments were made on 2 year old tadpoles of the bullfrog, *Rana catesbeiana*, and of 1 year old tadpoles of the green frog, *Rana clamata*. The experimental tadpoles were fed on 7 parts  
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of flour plus 3 parts desiccated prostate substance. The controls were fed on flour made into a paste. At the conclusion of the experimental period, the length of the intestine of paired specimens of control and prostate-fed tadpoles was compared and the results recorded in centimeters. In every case the intestine of the experimentally fed tadpole was shorter than that of the control. The average length for the controls was 37.3 cm. and for the prostate-fed specimens 25.7 cm.

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**The Structure and Differentiation of the Specific Cellular Elements of the Pars Intermedia of the Hypophysis of the Domestic Pig.**

*Siegfried Maurer and Dean Lewis, J. Exper. Med., 36:141, July 1, 1922.*

A review of the literature confirms the presence of pressor substance in pars intermedia, but its relation to the colloid material of the pars intermedia or to the hyaline and granular mass of the pars nervosa requires further elucidation. The solution of this problem was accomplished by answering the following: Firstly, can the pars intermedia be identified as a physiologic entity by its specific chemical products? Secondly, is there any correlation in the embryo between the time of appearance of pressor activity in the hypophysis and the specific product of the pars intermedia cells? In addition to morphologic studies, observations were made as to the precipitability, tinctorial and microchemical reactions of the products of activity of the glandular cells. Adult and embryonic hypophyseal material was obtained at the abattoir soon after the sacrifice of the hog and with a minimum of trauma to the gland. Pig embryos were similarly studied. Two types of cells can be recognized in the pars intermedia. The one is a cubical or columnar, colloid-producing cell with basal nucleus and poorly stained cytoplasm. These cells line follicles containing transparent colloid. An actual, sluggish secretory activity is indicated by the presence of small droplets of colloid in the cell proper. The major part of the pars intermedia consists of a second type or granular cell of varying prismatic shape and with eccentric or polar nucleus. Alongside the nucleus or at some distance from it may be found a mass of deeply staining cytoplasm free from secretion, presumably containing the sphere and centrioles. The individual cells contain various amounts of a highly labile secretion which appears as small, poorly stained granules. These granules are not found in the juxtannuclear deeply staining cytoplasmic mass. The granules disappear more rapidly postmortem and are more soluble than any similar tinted bodies of the anterior lobe cells. These granules are distinguishable from those of other granule bearing cells of the hypophysis by their size, diffuse distribution and characteristic tinctorial reactions. The staining methods of choice for differentiating these various granules are acid fuchsin-acid violet, neutral safranin-acid violet, and the neutral gentian method of Bensley.

The cells of pars intermedia of pig embryos measuring 7.5 cm. have large nuclei and little cytoplasm with ill-defined outline. Studies of older embryos show gradual development of the granule bearing cell similar to that of the adult pars intermedia. Hyaline bodies were not

found in any of the fetal hypophyses. Serial sections are necessary to discover colloid containing vesicles in the pars intermedia of 7.5 cm. pig embryos. The follicles if found are lined by cylindrical cells with clear nongranular cytoplasm and basal nucleus. Extracts of hypophysis of similar sized pig embryos are inactive as regards pressor effect, regardless of the number of glands used in the preparation of the extracts. The appearance of the pressor effect is synchronous with development of the granules or secretory antecedent of the pars intermedia.

The study reveals the presence of a true secretory antecedent in the cells of the pars intermedia, the resultant secretion leaving the gland by way of the vascular route rather than by way of the interfibrillar spaces of the pars nervosa. The so-called pressor effect of the pars nervosa of the posterior lobe can be accounted for by difficulty in mechanical separation of this portion and also by the rapid diffusion, postmortem, of the highly soluble secretion of the pars intermedia.

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**The Effect of Adrenalectomy upon the Total Metabolism of the Cat.**

*Joseph C. Aub, Jonathan Forman and Elizabeth M. Bright, Am. J. Physiol., 61:326, July 1, 1922.*

The work here reported was undertaken to study more thoroughly the possible independent relationship of the adrenal glands to the control of the metabolic rate. An attempt was made to keep the cats in excellent condition, with normal body temperature and normal blood pressure, and to control all abnormal factors which developed during operation, in order to determine whether the mere removal of the secretion of the adrenal glands would affect the metabolic rate of the organism. Under ether anesthesia the adrenalectomies were usually done in one stage, the posterior route being selected. The tabulated and graphic data show that 48 hours after the removal of both adrenal glands there is a reduction of about 25% in the total metabolism without marked change in the relative percentages of foodstuffs burned. This drop in the metabolic rate was evident when measured as total calories, or calories per kilo of body weight. Control experiments on completely fasting and operated cats showed a fall in metabolism less than half the magnitude of that seen after adrenalectomy.

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**The Metabolic Effect of Adrenalectomy upon the Urethanized Cat.**

*Joseph C. Aub, Elizabeth M. Bright and Jonathan Forman, Am. J. Physiol., 61:349, July 1, 1922.*

Observations of previous workers suggested to the authors that adrenalin is secreted more rapidly under urethan anesthesia than under normal conditions; that the effects of adrenalectomy upon the metabolism of the cat might be more readily observed in a urethanized animal than in the unanesthetized animal, where such effects appear only at the onset of the symptoms due to adrenal insufficiency. A series of

experiments was therefore performed on urethanized animals, employing a procedure similar to that described by Aub in the study of basal metabolism in traumatic shock. The resulting tabulated data show that after removal of the adrenal glands under urethan anesthesia, there is a prompt and progressive fall of metabolism which averages 12%. An increased flow of adrenalin was also observed under urethan anesthesia. Adrenalin injected intravenously at a physiologic rate caused a distinct rise in the metabolism which leads to a tentative conclusion, that in these experiments the fall in metabolism after adrenalectomy was due to the lack of the usual adrenal secretion.

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**Studies on the Conditions of Activity in Endocrine Glands. XI. Further Evidence for Reflex and Asphyxial Secretion of Adrenin.**

*W. B. Cannon and R. Carrasco-Formiguera, Am. J. Physiol., 61:215, July 1, 1922.*

The most discriminating method of demonstrating splanchnic control of the adrenin output is that employed by Stewart, Rogoff and Gibson. In the experiments described in this paper the authors have undertaken to retrace, as far as possible with reflex stimulation, the steps taken by Stewart, Rogoff and Gibson in direct splanchnic stimulation. In the procedures, cats were used, under ether or chloralose anesthesia. The hepatic factor was invariably eliminated by section of the hepatic nerves.

The authors claim that after severance of the hepatic nerves the acceleration of the denervated heart when an afferent nerve is stimulated is due solely to the passage of adrenin from the adrenal glands to the heart. In support of this statement they submit the following evidence: (1) If the venous path from the adrenal glands is blocked in such manner that the only change is a shutting of adrenal blood out of the circulation, the reflex response, which previously occurred, is prevented. (2) After removal of the venous block the reflex response can again be obtained and the released blood (adrenal) causes a greater cardiac acceleration than if, during the block, an afferent nerve has not been stimulated. (3) If the free flow through the inferior cava is stopped above the opening of the lumbo-adrenal veins, the typical reflex response fails; the time interval between release of the pent blood and the effect on the heart is approximately the same as that between the start of afferent stimulation and the effect on the heart. (4) The time interval between the start of reflex stimulation and the beginning of the cardiac response is approximately the same as that seen after exciting a splanchnic nerve or injecting a physiologic amount of adrenin into a femoral vein. Asphyxia for 45 seconds induces a more rapid beat of the denervated heart. This effect fails if the passage of blood away from the adrenal glands is prevented, and appears when the blood is released.

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**The Production of Adrenal Discharge by Piquê.**

*R. Carrasco-Formiguera, Am. J. Physiol., 61:254, July 1, 1922.*

All the author's experiments were performed on anesthetized cats.

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The heart was denervated according to Cannon's directions. Artificial respiration, started previous to opening the thorax, was continued until the end of the experiment in order to prevent any respiratory disturbance that might arise from injury to the medulla and mask the changes of heart rate properly due to piqûre. Blood pressure and heart beats were recorded from a femoral or carotid artery; time was recorded in 5-second intervals. Piqûre was performed by an adaptation to cats of Eckhard's technic for rabbits. Author shows: (1) that piqûre increases the rate of the denervated heart; (2) that piqûre increases the rate of the denervated heart after section of the hepatic nerves; (3) that piqûre does not result in increased heart rate when, after exclusion of the hepatic factor, one adrenal is removed and the other is completely tied off; and (4) if after exclusion of the hepatic factor, the venous exit from the adrenals is temporarily occluded, piqûre is not followed by an increased heart rate, but the rate increases when, some time after the puncture, the venous block is removed without any other change in circulatory conditions. Author concludes that Bernard's puncture of the floor of the fourth ventricle produces the discharge from the adrenal glands of a product that reaches the arterial blood in sufficient amount to exert on other organs an action identical with that of adrenalin.

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**Changes Produced in the Larval Brain of *Rana Pipiens* by Thyroid Feeding.**

*Warren B. Cooksey, Endocrinology, 6: 393, May, 1922.*

Armour's thyroid powder, mixed with powdered clover leaves and flour, was fed twice a day to a large series of frog tadpoles. In the control food, powdered egg yolk was substituted for thyroid powder, to make up the deficiency in protein. Experimental and control tadpoles were carefully matched in size. A few were kept on a thyroid diet for 40-60 days, thus becoming almost completely metamorphosed. The thyroid accelerated metamorphosis. It was also shown that the tadpoles fed in the late fall were more resistant to the toxic action of the thyroid hormone than those fed in the early summer; and those fed in the summer had a much higher rate of metamorphosis than those fed in winter. The larger tadpoles survived longer and metamorphosed to greater extent than the smaller ones. The seasonal effect may be due to the accelerated metabolism during the summer months and the greatly increased glandular activity, all of which would result in an increased susceptibility to thyroid feeding.

As to brain structures, the extent of metamorphosis depends somewhat on the length of time the tadpoles are able to live and feed on thyroid, and on the season of the year. However, there was a uniformity of change. The body length decreased 15.89% while the brain length increased 1.76%; the fossa rhomboidalis was much shortened; the cerebral hemispheres lost their globular form; the anterior lobe of the hypophysis was diminished in size; and other changes closely resembling those of normal metamorphosis were seen. Many striking abnormalities were produced in various parts of the brain, caused by pressure from surrounding structures. These were due to abnormal differential rates of growth.



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**Studies upon the Mechanism of the Increased Metabolism in Hyperthyroidism.**

*Joseph C. Aub, Elizabeth M. Bright and Joseph Uridil, Am. J. Physiol., 61 : 300, July 1, 1922.*

These experiments were undertaken to study further the mechanism of the increased heat production after thyroid ingestion, to see whether muscular movements, the fibrillation of muscles, muscle tonus, or adrenal secretion could be its cause, or whether it was necessary to assume that the general basal rate of cellular combustion was raised. The experiments were performed on cats and the methods used to determine the metabolic rate were the same as those previously described by the authors. After the basal metabolism had been carefully determined, a solution of crystalline thyroxin was injected in doses of approximately 3 mg. a day, until the metabolic rate was markedly raised. The effects of adrenalectomy and of cutting the sacral and brachial nerve plexuses were then studied, and the results compared with those obtained from animals which had received no thyroxin. The data accumulated, the authors have recorded in the form of charts which show that urethane anesthesia causes a rise in the metabolism of thyrotoxic animals as it does in normal animals. By severing all involved nerve supply the authors were able to show that the increased basal metabolism stimulated by thyroxin cannot be explained by muscular activity, muscular fibrillation or increased muscle tonus. They also found that the adrenal glands are not essential to the maintenance of a high metabolic rate induced by thyroxin. Authors' findings support the theory that thyroxin stimulates resting cells to a higher level of metabolism.

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**1b. BIOLOGIC AND ORGANIC CHEMISTRY**

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**Osmotic Pressure; Its Significance and Its Regulation in the Animal Body.**

*Emil Reiss, Klin. Wchnschr., Berlin, 1 : 1083, May 27, 1922.*

Osmotic pressure is a matter of comparative density. Osmotic pressure develops when 2 solutions of different concentration are separated by a membrane which is permeable by the solvent but impermeable by the dissolved substance. The osmotic effectiveness of a dissolved substance depends on the number of molecules to the unit of weight. The osmotic pressure of a solution is dependent on the number of molecules and the dissociability, as each ion has the same osmotic activity as the molecule. Therefore electrolytes have almost twice as great an osmotic pressure as would be indicated by their molecular weight, while proteins, for instance, with their high molecular weight and low dissociability cause practically no osmotic pressure. But for practical osmotic pressure the decisive point is how closely the separating medium between the 2 fluids approaches the ideal of a semipermeable membrane. Such ideal membranes scarcely occur in the animal body, and therefore in the living organism we cannot summarily attribute differences of concentration to osmotic pressure of a certain degree, such as would

take place through an ideal membrane. While the blood and tissue fluids show a constant osmotic pressure, this is not true of the secretions and excretions, and therefore osmotic pressure has been regarded as the most important impelling force in secretion, resorption and excretion of urine.

If excretion of urine were caused by osmosis between the glomeruli and urinary tubules, it would be impossible to explain the excretion of urine which is generally hypertonic, in the production of which the kidney withdraws certain dissolved substances from the blood without the osmotically corresponding amount of water. Kidney activity therefore produces a difference in osmotic pressure, instead of the production of urine being the result of osmotic forces. As there is no ideal semipermeable membrane in the kidneys it is impossible to calculate the functional capacity of the kidney from the osmotic differences between blood and urine.

In intestinal resorption osmotic pressure is an impelling force only in the taking up of water from hypotonic solutions and the taking up of dissolved substances from hypertonic solutions. Experiments have shown that processes of osmosis and diffusion do take place in the intestine, but that they may act contrary to resorption as well as in the direction of supporting it. Therefore in addition to osmotic pressure there must be other forces in action to make the intestinal contents approach the osmotic pressure of the blood. Isotonic solutions are best absorbed, in which the coöperation of osmotic force is not necessary. If the solutions are not isotonic there is no resorption; on the contrary, fluid passes into the lumen of the intestine. Osmotic pressure therefore is not necessary as the impelling force in resorption. The normal course of cell processes is however connected with a certain osmotic pressure. Blood, plasma, lymph, spinal fluid, the aqueous humor of the eye, and the seminal fluid have under physiologic conditions a constant, almost equal, osmotic pressure. Slight variations are the physiologic stimulus which activates the specific function of the cells. Greater pathologic differences result in disturbances of cell activity.

A very delicate regulatory mechanism is necessary to preserve physiologic isotonia, and this may be of peripheral or central origin. All kinds of cells may act as peripheral regulators, as the stimulus produced by the swelling and contraction of the cells may be propagated by the usual innervation of any given organ. The Vater-Pacini corpuscles (lamellar corpuscles) are regarded as special organs for peripheral osmotic sensibility, as their structure is particularly adapted for this function. Several centers for central regulation have been found in the floor of the fourth ventricle and at the base of the midbrain, which influence water and salt exchange in a specific way and which can be regarded as centers for osmotic pressure. These centers are not only connected by means of sympathetic and parasympathetic tracts which run in the vagus with all the organs which have to do with the excretion or retention of water and dissolved substances but they are also connected with intra-intestinal water and salt excretion and intermediate metabolism.

Under pathologic conditions man loses the capacity for maintaining normal osmotic pressure. In chronic nephritis there is a rise in osmotic pressure caused by the accumulation of products of metabolism in the

tissues; this is manifested by a lowering of the freezing point to  $-0.62^{\circ}$  C. instead of  $-0.56^{\circ}$ . In absolute kidney insufficiency with acute uremia, the osmotic pressure rises enormously and the freezing point sinks to  $-0.75^{\circ}$ . As the regulatory mechanism has failed, it is impossible to overcome the hyperosmosis even by vigorous measures to produce dilution.

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**The Making of Collodium Sacs.**

*Nathan Muskin and Louis Siegel, J. Lab. & Clin. Med., 7:564, June, 1922.*

The greatest difficulty in making dialysis membranes is the separation of the collodium sac from its glass mold. The following technic has been adopted to obviate this difficulty: Place a small collar of paper 1 in. wide in the mouth of the tube before adding the collodium. Then fill the tube with collodium. The collodium is then poured off and the tube allowed to dry for a few minutes while inverted. The tube is then placed in the  $55^{\circ}$  C. thermostat for  $\frac{1}{2}$  hour, or at room temperature for several hours, to allow the collodium to dry. The paper collar is then gently pushed in at some point and distilled water poured in between the collodium sac and the container. As soon as the container is full of water the sac can be easily removed. The paper collar is a convenient handle for the sac, both in the separation from the glass mold and afterward.

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**Distribution of Acidity in the Cell.**

*K. Spiro, Klin. Wchnschr., Berlin, 1:1199, June 10, 1922.*

It is possible, with 2 fluids that do not intermix, though a typical colloid substrate is not necessary, to construct a simple macroscopic model of the microheterogeneous balance that characterizes the cell. For the fundamental question of ion distribution in the cell protoplasm it is indispensable to have a system of very simply combined phases which can coexist and which are made up of the same building materials but in different proportions. For the most reactive hydrogen and hydroxyl ions it must be assumed that their concentration is not uniform in the cell as in a solution, but rather that it is different at different places.

For demonstration author uses a transparent model, placing a layer of liquefied phenol over an aqueous solution of phenol. If after the addition of phenolphthalein a little alkali is carefully added, only the aqueous layer shows a red color, that is, an excess of hydroxyl ions. If a mixture of 10 c.c. saturated phenol solution and 2 c.c. liquefied phenol is shaken up with 1 c.c. of 0.1 n. sodium hydroxid, 2 layers are formed which may be brought to the same concentration; if equal volumes of rosolic acid are added to both layers, the original phenol solution is weakly acid; the alkali has accumulated in the aqueous layer. In this way it can be shown that the ion distribution, especially that of the hydrogen and hydroxyl ions, is dependent on the water content, or on the relation between the solvent and the dissolved substance, particularly in the coexistent phases, and therefore with the assumption

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of an unequal water distribution the different reaction of the different cell phases may be regarded as experimentally proved.

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**The Hydrogen-Ion Concentration of Human Feces.**

*C. S. Robinson, J. Biol. Chem., 52:445, June, 1922.*

The author determined the normal fecal reaction of normal human subjects on mixed diets. The determinations of the pH were made electrometrically, the general technic and apparatus described by Clark being used. The reaction was found to lie between pH 7.0 and 7.5. The effect of the following laxatives on the fecal reaction was studied: magnesium oxid, phenolphthalein, physiologic salt solution, castor oil, aloes, senna, and sulphur. The usual result was the production of an acid stool. Administration of the alkali, magnesium oxid, does not differ from the others in this respect, but the fecal material passed after the cessation of the laxative action was unusually alkaline. No result was observed by the author from the introduction of acidophilic bacteria into the intestine.

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**Hydrogen-Ion Concentration.**

*C. W. O. Bunker, U. S. Naval M. Bull., 16:973, June, 1922.*

Unfortunately the usual presentation of this subject is either too cursory or too technical. As is well known an electric current passed under proper conditions through a solution of a metallic salt will cause decomposition of the metal at one electrode. This phenomenon, known as electrolysis, is the basis of the familiar process of electroplating and is merely a special manifestation of ionization. The portion of the salt from which the metal has been detached travels to the other pole, thus, the salt has been decomposed into 2 portions, or ions—one the metal of cation, bearing a positive charge of electricity and going to the negative pole, while the other, or anion, bears a negative charge and collects at the positive pole. For this separation into ions, however, an electric current is not a necessity, for the molecules of a large number of chemical compounds partially dissociate into ions upon being placed in solution, and one ion will carry a charge of positive while the other carries one of negative electricity. Under definite conditions, the degree of dissociation is constant. Concentration is a common chemical term and means the weight (in grams) of the substance per liter of solution. In the present connection the term is used with regard not only to the original compound placed in solution but also to the portion that remains undissociated in the solution. The results of this dissociation, the ions, are definite forms of matter, have weight, and are present in a definite concentration. Consequently, by pH is meant the weight of hydrogen in ionic form present in a liter of solution.

The solutions ordinarily employed are aqueous. The solution of an acid in water adds H-ion, thereby diminishing the OH-ion. The solution of a base in water increases the OH-ion and diminishes the H-ion. As the H-ion increases the OH-ion decreases, and vice versa, and the acid and basic factors are thus seen to bear a definite relation to each other. There is always some dissociation of the water, and aqueous acid solutions contain some OH-ion just as aqueous alkaline

solutions contain H-ion. It has become customary, for convenience, to consider only the H-ion, even alkaline solutions being described in terms of pH. The excretions—urine, sweat, feces, etc., the digestive juices, cerebrospinal fluid, serous fluids, blood, etc.—have been investigated relative to pH. It is involved in the question of hemolysis, and the very important one of acidosis. A clear understanding of the meaning of pH is necessary to any medical man who endeavors to comprehend the metabolic processes of the human body. It is indispensable to the bacteriologist and other workers with manifestations of vital phenomena.

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**A Comparison of Colorimetric and Electrometric Determinations of Hydrogen-Ion Concentrations in Solutions Containing Carbon Dioxid.**

*Glenn E. Cullen and A. Baird Hastings, J. Biol. Chem., 52: 517, June, 1922.*

In connection with the development of a colorimetric method for measuring the reaction of the blood it became important to determine the precision of the colorimetric method as compared with the electrometric method when used with solutions containing carbon dioxid. Experiments were therefore carried out on solutions of sodium bicarbonate which had been equilibrated with known tensions of carbon dioxid and in a similar manner on solutions of sodium bicarbonate plus sodium phosphate. The colorimetric readings were made under paraffin oil in the manner described in a preceding paper, except that the solutions were not diluted. Phenol red was used in preference to neutral red because of the marked tendency of neutral red to precipitate out of solution. Sorensen's phosphate standards were prepared at intervals of 0.05 pH and the readings were made to 0.01 pH. The electrometric determinations were carried out with the same technic and precautions previously described. The tabulated results show that when both colorimetric and gasometric measurements of pH are carried out by the technic described, there is complete agreement between the 2 methods in both carbonate and phosphate-carbonate solutions.

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**A Modification of the Clark Hydrogen Electrode Vessel to Permit Accurate Temperature Control.**

*Glenn E. Cullen, J. Biol. Chem., 52: 521, June, 1922.*

The author has devised a modification (illustrated in the article) of the Clark cell to permit the insertion of a thermometer into the solution. This eliminates the practice of using the temperature of the open room in which the cell is placed, as the temperature of the solution. This latter procedure has been found to result in errors of 0.01-0.03 pH.

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**On the Measurement of Buffer Values and on the Relationship of Buffer Value to the Dissociation Constant of the Buffer and the Concentration and Reaction of the Buffer Solution.**

*Donald D. Van Slyke, J. Biol. Chem., 52: 525, June, 1922.*

Buffers are substances which by their presence in solution increase  
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the amount of acid or alkali that must be added to cause unit change in pH. The most efficient buffers, at reactions within the usual range of biologic significance, are mixtures of weak acids or weak bases and their salts. Their buffer effect is due to the relatively slight extent to which they undergo electrolytic dissociation, as compared with the almost completely dissociated strong acids and bases. As a numerical measure of the buffer value of a solution the number of gram equivalents of strong alkali or acid taken up per unit change in pH has been used by the author. In these terms, each cubic centimeter of normal alkali or acid that must be added to a liter of solution to raise or lower its pH by 1 adds 0.001 to the buffer value.

(The article includes so many detailed mathematical formulas that reference to the original work is suggested.)

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**Calcium Fixation by Animal Tissues.**

*F. Freudenberg and P. György, Biochem. Ztschr., Berlin, 129: 134, 138, April 19, 1922.*

According to Loeb's theory, with a given H-ion concentration, an amphoteric colloid is assumed to form either only cations or only anions. That is determined by the system's H-ion concentration and by the position of the iso-electric point of the amphoteric colloid. To elucidate this question, ultrafiltration experiments, and, regarding anion action, intumescence experiments, were undertaken, which confirmed the previous finding that there is an influence of the anions on the combination of calcium with tissue colloids which is not referable to H-ion action. The combination is weaker with chlorid than with acetate, nitrate, phosphate and bicarbonate. The arrest of combination by nitrogenous organic substances was also established by means of intumescence experiments.

Amino-acids are able, presumably, to bind calcium and thereby to withdraw calcium ions of the solid phase (cartilage in the experiments). Arrest will take place by the chemical union of substances having an amin character, such as guanidin; the radicals of the proteins destined for calcium ions are replaced by the respective organic substances and calcium combination does not take place. The action of formaldehyd depends on the combination of the  $\text{NH}_2$  radical of free amino-acids. Having regard to this behavior experiments were carried out with formaldehyd, acetone and ethyl alcohol, in which compensatory dialysis was employed. The results were as follows: Formaldehyd and glucose arrest combination of calcium to cartilaginous tissue, while ethyl alcohol and acetone in a 0.1 n. concentration do not affect the same. The reaction velocity of calcium fixation increases with rising temperature. Thereby a further proof of the chemical character of the binding calcium to animal tissue is supplied.

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**A Colorimetric Method for the Determination of Small Amounts of Magnesium.**

*A. P. Briggs, J. Biol. Chem., 52: 349, June, 1922.*

Colorimetric methods for the determination of phosphorus in blood and urine have recently been published by Bell and Doisy, based  
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upon the selective reduction of phosphomolybdic acid by hydroquinon in the presence of excess ammonium molybdate. In the method here described, use is made of the principle of their method for the determination of the phosphorus content of precipitated  $\text{MgNH}_4\text{PO}_4$ . The method is obviously applicable to any substance from which  $\text{MgNH}_4\text{PO}_4$  may be precipitated.

**Procedure:** By means of a pipette, transfer a measured volume of the plasma into a small flask, dilute with 3 volumes of water and 1 volume of 20% trichloroacetic acid, mix by shaking, and pour onto an ashless filter. Transfer 15 c.c. of the filtrate into a 25 c.c. pyrex test-tube. Add 1.5 c.c. potassium acetate solution and 2 c.c. ammonium oxalate solution; rub up and down inside the tube with a rubber-tipped rod until the  $\text{CaC}_2\text{O}_4$  seems to be completely precipitated and rinse off the rod with a little water. Heat the tube 15 minutes in a boiling water-bath, and after cooling to room temperature centrifugate for 5 minutes at about 2000 r. p. m. Pour the supernatant liquid from the calcium precipitate into a 50 c.c. centrifuge tube. Add 1 c.c. ammonium phosphate solution and 5 c.c. concentrated ammonia and rub up and down inside the tubes with a rubber-tipped rod until precipitation seems to be complete. After standing 3 or 4 hours, centrifugate for 10 minutes at about 1500 r. p. m. and pour off the supernatant liquid. Fill the tubes about half full with the ammoniacal alcohol wash solution, and rinse down the sides of the tube carefully with a jet of the same solution from a wash bottle. Centrifugate 5 minutes and pour off the wash fluid, wash a second time in the same manner. Dissolve the precipitate in 5 c.c. normal sulphuric acid, add 1 c.c. molybdate solution and 1 c.c. hydroquinon solution, and dilute with water up to the graduation mark at 20 c.c. Prepare a standard at the same time containing 5 c.c. standard magnesium solution and the same amounts of sulphuric acid, molybdate, and hydroquinon. Mix the solutions and after 5 minutes compare in the colorimeter.

The solutions used are: (1) Standard magnesium solution, containing 0.1413 gm.  $\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$  per liter in 0.01 n. sulphuric acid, preserved by the addition of 2 c.c. chloroform. Of this solution, 5 c.c. are equivalent to 0.07 mg. magnesium which is about the amount found in 3 c.c. of plasma. (2) Molybdate solution, containing 5% ammonium molybdate in 1 n. sulphuric acid. (3) Hydroquinon solution, containing 2% hydroquinon. (4) Potassium acetate solution, prepared by dissolving 125 gm.  $\text{K}_2\text{CO}_3$  in as little water as possible and allowed to stand over night; filter and neutralize with 100 c.c. glacial acetic acid, and dilute to 500 c.c. with water. This solution was found to be free from calcium and magnesium. All available samples of sodium acetate were found to contain calcium or magnesium. (5) Ammonium phosphate, 2% solution  $(\text{NH}_4)_2\text{HPO}_4$ , preserved with chloroform. (6) Ammonium oxalate, a saturated solution. (7) Ammoniacal alcohol, containing 200 c.c. of 95% alcohol and 50 c.c. concentrated ammonia per liter.

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**Micromethods of Urine and Blood Analysis.**

*Hsien Wu, China M. J., Shanghai, 34: 121, March, 1922.*

Owing to the expense of equipment and maintenance the laboratory  
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cannot soon be expected to become an integral part of the hospitals of China. The 2 problems which the clinicians here have to solve are where to procure the needed apparatus and how to modify methods when gas and running water are not available.. Since it is difficult to get a pure creatinin zinc chlorid in the market it is well to know that a standard solution of creatinin suitable for use in urine, and (when diluted) in blood analysis, can be prepared from normal urine. To 500 mils normal urine add 10% sodium hydroxid solution until it is distinctly alkaline to litmus and then add 5 mils more; allow to stand 5-10 minutes and filter off the phosphates; add 10% HCl until it is distinctly acid. Determine the creatinin content in this solution and on the basis of this determination prepare a solution containing exactly 1 mg. creatinin per mil or, if the urine is too dilute, 0.5 mg. per mil. From this standard solution for urine analysis a weaker solution for blood analysis containing 6 mg. creatinin per liter is prepared. Uric acid of sufficient purity can also be prepared from urine.

It is very difficult to make a nitrogen determination by the macro-Kjeldahl method without gas, but good results can be obtained by using an alcohol lamp. Since alcohol lamps cannot be adjusted, the author has found it convenient to use 2 alcohol lamps for each digestion, one with a large wick for the preliminary evaporation, and when the water has been driven off, this lamp is replaced by another with a small wick. One way of obtaining a short, pointed flame is to place a conical glass or metal cap over the wick, which projects a little above it. In the determination of the urea in urine by the method of Folin and Youngberg, the soy bean may be used instead of the American Jack bean. As the soy bean contains a higher percentage of protein it is necessary to use stronger alcohol (40%) and to allow a longer time for the action of the urease on the urea. In the absence of gas and running water the only convenient way of determining urea in blood is by the method based on urease action and distillation. The essential in this method is that the liquid should boil gently while the ammonia is being distilled. To insure this, the wick of the alcohol lamp should be trimmed to a pointed tip close to the metal tube, to produce a short steady flame. In the first part of the distillation the liquid should not be heated too strongly.

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**A Method for the Direct Determination of Uric Acid in Urine.**

*Stanley R. Benedict and Elizabeth Franke, J. Biol. Chem., 52: 387, June, 1922.*

For the direct determination of uric acid in urine, required solutions are: (1) The reagent, which is the one used in the new procedure of Benedict for the direct determination of uric acid in blood. It is prepared by placing 100 grams of pure sodium tungstate in a liter pyrex flask, dissolving in about 600 c.c. water, and adding 50 gm. pure arsenic acid ( $\text{As}_2\text{O}_5$ ), followed by 25 c.c. 85% phosphoric acid and 20 c.c. concentrated HCl. The mixture is boiled for about 20 minutes, cooled and diluted to 1 liter. (2) Sodium cyanid, a 5% solution, prepared fresh every 2 months, is used. (3) Uric acid of which a standard solution acidified with HCl, containing 0.2 mg. of uric acid in 10 c.c., is employed.

**Procedure:** The urine is diluted so that 10 c.c. will contain between 0.15 and 0.30 mg. uric acid. Usually a dilution of 1:20 will suffice. Then 10 c.c. of the diluted urine are measured into a 50 c.c. volumetric flask and 5 c.c. of the 5% sodium cyanid solution are added from a burette, followed by 1 c.c. of the arsenophosphotungstic acid reagent. The contents of the flask are mixed by gentle shaking, and at the end of 5 minutes diluted to the 50 c.c. mark with distilled water and mixed. This blue solution is then compared in a colorimeter with a simultaneously prepared solution obtained by treating 10 c.c. standard uric acid solution (0.2 mg. of uric acid) in a 50 c.c. flask with 5 c.c. sodium cyanid solution and 1 c.c. of the reagent, and diluting to the mark at the end of 5 minutes. For the calculation the reading of the standard (15 or 20 mm.) divided by the reading of the unknown, and the result multiplied by 0.2, gives the milligrams of uric acid contained in the 10 c.c. diluted urine used in the unknown.

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**Variations in the Diastatic Power of the Urine in Relation to Its Reaction, with a Suggested Method for the Estimation of the Diastase Content.**

*B. C. Dodd, Brit. J. Exper. Path., London, 3:133, June, 1922.*

In the author's inquiry into the effect of reaction upon urinary diastase, the first investigation carried out was the fixing of the optimum pH. Since buffer solutions of varying reaction can be easily made with mixtures of phosphates, the optimum pH of the phosphate diastase compound in urine was determined by taking a quantity of urine and diluting it 1:5 with buffer solutions of varying pH and the diastatic power obtained by the method described below. The tabulated results show 6.1 to be the optimum pH for the phosphate diastase compound of the urine.

The solutions required in the author's method are: (1) A 0.2% starch solution, best made by adding the weighed quantity of starch pinch by pinch to the requisite volume of distilled water, and stirring until an even suspension is obtained. The mixture is then slowly brought to a boil, stirring all the time. After boiling for a short time the solution becomes opalescent, when it is cooled and the volume is made up to the correct amount. This solution should be made fresh daily. (2) Phosphate buffer solution, obtained by mixing 15 c.c. of Sorensen's solution A with 85 c.c. solution B. Solution A is made by dissolving 11.876 gm.  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  in 1 liter of boiled distilled water, the solution being kept in a paraffin-coated bottle. Solution B is made by dissolving 9.078 gm. of  $\text{KH}_2\text{PO}_4$  in 1 liter of boiled distilled water, and is stored in a paraffin-coated bottle. The resulting solution should have a pH of 6.1. In the method 1.5 c.c. urine are added to 6 c.c. buffer solution and the resulting solution shaken well to insure uniform distribution. Several test-tubes are then prepared, in each of which is put (in varying quantities) 0.2% starch solution, buffered urine and distilled water. The urine and the fractions of a c.c. of water are added first, followed by the starch solution. Then 1 c.c. water is added to each tube except the first. The tubes are incubated for half an hour at 37° C., cooled, and 0.5 n. iodine added in such a quantity as will just give

a faint color. In calculating the results the author assumes that the tube just failing to show a mauve tint, i. e. the one where the starch was just digested, contains 0.5 c.c. diluted urine. Therefore 0.5 c.c. of diluted urine, or 0.1 undiluted urine, just digests 1 c.c. of 0.2% starch, or 2 c.c. of 0.1% starch. Since the number of Wohlgemuth's units is expressed by the number of cubic centimeters of 0.1% starch solution digested by 1 c.c. urine, it is obvious that in the above case 20 units of diastase were present.

Ammoniacal decomposition, by making the urine more alkaline, decreases the diastatic power as determined by the old method but has no effect on the method suggested. The author recommends that all urines be well shaken before the estimation is performed since diastase clings to urinary deposits.

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**On a Possible Asymmetry of Aliphatic Diazo-Compounds. II.**

*P. A. Levene and L. A. Mikeska, J. Biol. Chem., 52:485, June, 1922.*

In the author's experimental work Van Slyke's amino-apparatus was used. For this purpose a leveling bulb was connected to the lower outlet of the mixing chamber by a rubber tube, and filled with mercury. Before beginning the analysis the mixing chamber is filled with mercury. By lowering the leveling bulb a vacuum is created. Then 25% sulphuric acid is introduced into the mixing chamber and the diazo-derivative dissolved in a mixture of equal parts of isopropyl alcohol and water. On gentle shaking the operation is completed in about 2 minutes. The further procedure is the same as in Van Slyke's method for amino-nitrogen estimation. By this method diazo-ethyl acetate and diazo-ethyl succinamid were analyzed and the results tabulated. The author prepared diazodiethyl succinate and converted it into hydroxy succinate. He also converted the former into monobromodiethyl succinate. A description of the conversion of diazodiethyl succinate into monochlorodiethyl succinate is given in the article, as well as very detailed tabulated data and mathematical formulas.

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**Metacholesterol and Its Secondary Products. III.**

*I. Lifschütz, Biochem. Ztschr., Berlin, 129:115, April 19, 1922.*

Metacholesterol is obtained by the action of benzoyl peroxid on cholesterol in alcoholic solution. The yield amounts to 80%. A characteristic property of metacholesterol is its hydrophilous behavior in its mixtures with water-repelling fats, which serves for its detection in natural lipid bodies. If the unsaponifiable part of the same takes up more than 40% water from the mixture when melted with 2% pure white vaselin the presence of considerable amounts of metacholesterol is certain. On allowing the aqueous alcoholic filtrate of this metacholesterol to stand some time, a crystalline precipitate forms which represents oxycholesterol. Metacholesterol can also be prepared by the dry method by heating cholesterol in the oilbath to about 150° C. On cooling to 112°, about 60% elliptic scales separate and about 35% that remain in the alcoholic filtrates after filtering off metacholesterol are amor-



phous oxysterol. With digitonin only crystalline sterols are precipitated but not the amorphous sterol oxides. Digitonin recrystallized from glacial acetic acid-alcohol yielded a strong sterol reaction but no oxysterol reaction with acetic-sulphuric acid. If light be allowed to act on sterol, it turns brown-yellow, the taste becomes bitter, the amorphous part (oxysterol) becomes larger and larger while the yield of crystalline metasterol diminishes.

Metasterolbromide was prepared by saturating completely a 10% etherial metasterol solution with a freshly prepared etherial bromine solution of equal strength and precipitating the bromine formed with 90% alcohol. The melting point was 93-94°. The molecular weight of metasterol was 369. Accordingly metasterol is to be regarded as isomeric with true rhombic sterol. The optical activity of metasterol is in agreement with that of true sterol.

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**A Study of Ester-Forming Yeasts.**

*Ulrich Weber, Biochem. Ztschr., Berlin, 129:208, April 19, 1922.*

Experiments are described that sought to determine the conditions under which the formation of fragrant esters takes place in some lower fungi. The question was dealt with by physiologic experimental methods. There were employed *Willia saturnus* Klöcker, *Willia odessa* n. sp., *Willia schneegii* n. sp., *Pichia suaveolens* Klöcker, *Oidium suaveolens* Krzemecki and *Siachsia suaveolens* Lindner. These organisms were raised in pure cultures in nutrient glycerin and mannite solutions under different conditions.

Results showed: In the observed yeasts and imperfect fungi the ester odor typical for normal cases is not developed under all conditions. Cases occur in which, in spite of the most abundant development, no ester formation takes place, as in the case of growth in a carbon dioxide atmosphere. Esters are formed only when the simultaneous fermentation of carbohydrates assumes the rôle of sugar fermentation and liberates the energy requisite for the decomposition of albumin. Addition of alcohol enables a qualitative alteration of the ester odor to be attained. The employment of different nitrogenous nutrient media achieves an alteration of the odor only when other amino-acids are thereby presented simultaneously. Following addition of leucine a distinct odor of amylester is perceived. The ester odor of the species here investigated, which is always observable under normal conditions, is therefore capable of being influenced experimentally both qualitatively and quantitatively, as it is possible to alter both the character of the odor and also to prevent its occurrence in spite of the best development of the fungus.

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**Studies of Autolysis. VIII. The Nature of Autolytic Enzymes.**

*H. C. Bradley, J. Biol. Chem., 52:467, June, 1922.*

In the author's experiments the procedure followed is that used in previous investigations in which the final stage of proteolysis is measured by titrating amino-acids. With trypsin present, the gland tissues

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studied (pancreas, kidney and liver) behaved alike. Initial cleavage measured by the trypsin reaction went on faster in alkaline than in acid mixtures. Under identical conditions, but without trypsin, the autolytic enzymes effect the least amount of initial cleavage, and in the case of beef kidney this may be actually zero. This is not merely a quantitative difference, but a genuine difference in kind. With trypsin present, amino-acids appear most rapidly in strongly alkaline mixtures, where autolytic digestion is practically at a standstill, when tested by the same criterion. By both methods the unaided tissue fails to show evidence of trypsin under just those conditions where trypsin acts best. If trypsin is not to be found under its own optimum conditions, one is justified in concluding that it is not there. In regard to the effect of pepsin, it is more difficult to devise a series of experiments which will serve to prove or disprove the presence of pepsin in a tissue. The fact that autolysis proceeds better with increasing acidity makes the hypothesis that the enzyme complex facilitating autolysis is a pepsin-erepsin mixture all the more tenable. If pepsin be added to a fresh tissue mixture, under varying pH, one finds that it increases autolysis to some extent over the whole range, but least at the optimum acidity for autolysis itself. At this concentration of acid the primary fragmentation of the native tissue proteins goes on so fast that the addition of pepsin does not markedly alter the picture as a whole.

The experiments show evidence of an ereptic type of enzyme, which digests the primary cleavage products of proteins to amino-acids, but which does not digest the native tissue proteins. This enzyme complex is active between the H-ion levels of pH 8 to 3—. It is completely inactive at pH 1+. It was present in abundance in the tissues studied, and is apparently not a limiting factor in the rate of autolysis under conditions met with in the body. There is also evidence of an enzyme complex which digests the acid salts of the tissue proteins between pH 7 and 3. It is completely inhibited at a H-ion level of pH 2.6 while pepsin remains active at a pH 1±. The author has designated it the primary protease of the tissue, since it catalyzes the initial cleavage. The action of this enzyme constitutes the limiting factor in the autolytic machinery, and its activity is in turn conditioned by the amount of acid produced.

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**The Ferments of the Digestive Organs of Scorpions.**

*E. Sarin, Biochem. Ztschr., Berlin, 129: 359, May 3, 1922.*

The ferments in the scorpions' digestive organs have been investigated repeatedly. The scorpions were chloroformed, the organs removed and liver and pancreas treated separately with glycerin and a few drops of toluol, when the examination for ferments was undertaken. Qualitative catalytic tests were made for amylase, inulinase, invertase, lipase, pepsin, trypsin and rennin. With the glycerin extract 0.3 c.c. oxygen could be liberated from  $H_2O_2$ . Catalysis was therefore evident. As starch was converted into dextrin and maltose and the liquid assumed a darker coloration upon addition of iodine, amylase was detectable. To determine inulinase 1% inulin solution was added, but Fehling's solution was not reduced by this mixture even after standing 3 days. Inulinase was therefore absent. As the extract from the

organs showed no rotation of the plane of polarization with 5% saccharose solution invertase was also absent. To determine lipase the glycerin extract was kept 24 hours in the thermostat with 10% olive oil emulsion. On titrating with 0.1 n. NaOH and phenolphthalein as indicator only the liver extract showed increased acidity and not the intestinal and pancreatic extract. Detection of pepsin was effected by adding acid glycerin extract solution to 10% alkaline gelatin solution. After 3 days the gelatin that had received additions of liver and pancreatic extracts had liquefied. The occurrence of pepsin in these two is therefore demonstrated. For trypsin detection neutral 10% gelatin solution with and without added 1% soda was employed. In accordance with Gross, Fuld and Michaelis 0.1 gm. casein with a few drops soda solution was dissolved, filtered and the glycerin extracts added, allowed to stand one hour at 37° and then 25% acetic acid added in drops. In the presence of trypsin the casein molecule is split, forming compounds that are not precipitated by acetic acid, while unaltered casein is precipitated by acid. All glycerin extracts gave a positive result for trypsin. Rennin was determined by diluting 10 c.c. milk with 90% water and adding 1 c.c. of 10% calcium chlorid solution. Of this mixture 5 c.c. received an addition of 20 drops of glycerin extract in a test tube. The mixture was transferred to a water bath at 40°. Rennin was detectable in the glycerin extract of the liver.

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**The Action of Toxins on an Enzymotic Process. VII. Metal Catalase and Catalase Action. A Comparative Study.**

*C. G. Santesson, Skandin. Arch. f. Physiol., Berlin, 42: 129, May, 1922.*

The production of oxygen from an  $H_2O_2$  solution of colloidal silver on the one hand and by muscle catalase from a frog's muscle on the other was studied comparatively under the influence of different substances. The substances used were NaCl, KCl, KBr, KI, KCN, KF, potassium rhodanid,  $K_2SO_4$ ,  $KNO_3$ ,  $KClO_3$ , sodium borate,  $CaCl_2$ ,  $BaCl_2$ , KOH,  $K_2CO_3$ , secondary sodium phosphate, HCl,  $HNO_3$  and boric acid. With an insufficient amount of material the quality of the catalyzer is of importance in the effect. The amount of oxygen developed in 30 minutes rapidly approaches a maximum; from 0.17-0.34 mg. colloidal silver the rise is only slow but it persists up to 6.7 mg. Frog muscle catalase behaves in the same way but with less regularity. But the latter shows a decrease in effectiveness in stronger concentrations, probably as a result of inhibiting influences of the albumin and certain electrolytes. The development of oxygen by colloidal silver increases greatly with increase of temperature; with muscle catalase the action increases up to 27°, then decreases gradually and after 46° more rapidly, becoming null at 60°. The influence of the electrolytes on the enzymotic effect is not of the same nature as silver sol and muscle catalase. In general the colloidal silver is more strongly influenced by the halogen alkalis, including rhodanids and cyanids; with KF the action is the same and with KCNS it is smaller for the metallic catalyzer. Of the remaining neutral salts  $K_2SO_4$ ,  $KNO_3$  and  $KClO_3$  have a stronger action on muscle catalase,  $CaCl_2$  and  $BaCl_2$  a stronger one on

colloidal silver. Of alkaline hydrates and salts with an alkaline reaction KOH,  $K_2CO_3$  and  $Na_2B_4O_7$  have a stronger action on the organic and  $Na_2HPO_4$  a stronger action on the inorganic catalyzer. HCl and  $H_3O_3B$  have a stronger action on colloidal silver, while  $HNO_3$  either has the same action on both or acts more strongly on muscle catalase. These actions are measured at the boundary concentrations. Strong concentrations of electrolytes in general inhibit the action of colloidal silver, in weak ones they increase the development of oxygen, with the exception of KBr, KCNS,  $KClO_3$ , HCl and  $H_3O_3B$ , while with muscle catalase a function-increasing action of slight concentrations is exceptional, and is only observed decidedly with  $K_2SO_4$ , KOH,  $K_2CO_3$  and  $Na_2HPO_4$ . The actions on the colloidal metal are more pronounced than those on muscle catalase. Also in the series of anions and cations arranged according to the intensity of their action there are considerable differences for the two catalyzers.

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**The Action of Toxins on an Enzymatic Process. VIII. The Volumetric Methods for the Study of Catalases.**

C. G. Santesson, *Skandin. Arch. f. Physiol., Berlin*, 42: 191, May, 1922.

Author gives a historic review of the development of the methods in use in the study of catalases and describes and analyzes his own method. This has decided advantages because of the ease with which the action of different substances is tested, as well as because of the great sensitiveness of the volumetric method, especially the constancy of the slight resistance during the entire experiment and the exactness attained by daily normal examinations. However it is not possible to prevent a certain supersaturation of the test solution with oxygen. This error can be avoided however by a suitable modification of the form of the container by Hammersten's method. Nor can the action of bacteria be entirely excluded; but it can be reduced to an imperceptible degree within 2-3 days by keeping the catalase-containing muscle plasma in the cold. But if kept at room temperature there is an increase of the catalase action due to bacteria. But this fact does not enter into comparative experiments with regard to the action of different substances on the catalase. The concentration of  $H_2O_2$  (0.211% = 0.062 normal) did not injure the catalase action.

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**1c. PHARMACOLOGY AND TOXICOLOGY**

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**The Mechanism of Drug Action: A Study in Pharmacodynamics.**

O. C. M. Davis, *Brit. M. J., London*, p. 11, July 1, 1922.

The author brings together some scattered observations which help to throw light on the mechanism of drug action. A study of the toxic properties in relation to atomic weights indicates that the toxicity of an element belonging to the same periodic family is augmented with

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increase in atomic weight; such a law is subject to variations. A factor influencing pharmacologic activity is the solubility of a drug. In practical pharmaceutical chemistry, various methods are used to increase the solubility of compounds. Certain constituents of animal organisms exert a selective action in dissolving drugs introduced into the organism, thus certain tissues are specially affected. Vapor pressure influences the reactivity of a drug. Investigators have demonstrated the relationships between the chemical and physiologic reactivity of drugs; there is definite relationship between velocity of decomposition and degree of toxicity. It has also been shown that in certain cases chemical affinity and toxicity are quantitatively proportional. Toxicity must depend partly upon the relative velocities of formation of "cell-drug" compounds and excretion products. Regarding unsaturated valencies, generally open chain derivatives containing unsaturated carbon atoms are more toxic than isomeric saturated bodies. Many theories have been advanced regarding adsorption; experiments have led to the belief that it is important in pharmacologic action, and pathologic process. It is an undoubted fact that some people exhibit a marked intolerance towards certain drugs, while others may be able to tolerate abnormally large doses of some special drug. Such idiosyncrasies are inexplicable. Davis hopes that in the future chemistry and pharmacology will be more intimately associated, to the mutual advantage of scientists and clinicians.

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**The Effect of Pharmacodynamic Agents on Inflammatory Processes.**

*Hescheles and Progulski, Polska gaz. lek., Cracow, 1:485, June 11, 1922.*

By the intercutaneous action of a whole series of pharmacologic agents it is possible to produce specific pharmacodynamic effects which manifest themselves by the appearance of typical reactions. If 1 c.c. of a solution of these agents is injected through a needle introduced parallel to the surface of the skin, a wheal is formed, the appearance of which varies according to the substance injected. When adrenalin or pituitrin solutions are used there are sharply circumscribed blue protrusions; caffein solutions cause circumscribed hyperemias; but after the injection of alkaloids, peptone and extracts of organs there are urticaria-like wheals with stellate processes. The reaction is caused in the first case by vasoconstriction, in the second by vasodilatation, and in the third by the extravasation of lymph from the vessels.

The authors have studied the nature and course of these reactions, and also in those inflammations of the skin caused artificially by the injection of tuberculin and diphtheria toxins. Their conclusions are: (1) Agents which cause a local vasoconstriction have an inhibitory action on the course of the tuberculin reaction; these same agents strengthen the reaction to diphtheria toxin. (2) Agents which cause local vessel dilatation inhibit the diphtheria toxin reaction while they strengthen the tuberculin reaction. (3) Bodies which drive out lymph weaken and inhibit both reactions to a pronounced degree.

The intensity of the reaction caused by pharmacodynamic agents in a given individual is directly proportional to the concentration of



the solution, but it undergoes individual variations in different persons. To explain these phenomena, it may be assumed that the vasoconstriction influences the penetration of the secondary sensitizing factors developing at the site of injection of the tuberculin and therefore inhibits the full development of the tuberculin reaction. With diphtheria toxin this fact does not have inhibitory action for the action of the latter is primarily a toxic one. But by the contraction of the vessels the resorption of the toxin is made difficult and thereby its contact with the tissues is lengthened, making the reaction more intense. The inhibiting action of agents which cause extravasation of lymph is explained by the dilution of the tuberculin and diphtheria toxin by the extravasated lymph and by more rapid resorption.

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**Studies in Nonspecific Stimulation Therapy. III. Increased Action of Autonomic Nerve-End Toxins as a Reaction to the Alteration.**

*H. Freund and R. Gottlieb, Arch. f. exper. Path. u. Pharmacol., Leipsic, 93:92, May 2, 1922.*

Experiments on cats in ether narcosis. Preliminary treatment with caseosan, serum injection or venesection. The action of these procedures was evaluated by adrenalin experiments (determination of the lowest threshold value for bringing about a rise in blood pressure) and by pilocarpin experiments (determination of the secretion by weighing the cotton pledgets which took up the secretion from the salivary duct fistula). Results: Adrenalin sensitiveness could be greatly increased both by caseosan injection and serum injection. Often one-third to one-eighth of the usual amount was sufficient to cause a given rise in blood pressure. The reactive capacity was generally increased and this was observed even after 5 days. The same increase in adrenalin effectiveness was noted after venesection. In the pilocarpin experiments after the 3 methods of preliminary treatment 4 periods were demonstrated: (1) Preliminary period; increased secretion of saliva after pilocarpin (about 22 gm.). (2) Period during the injection of caseosan or homologous serum; the same secretion. (3) Six weeks after the treatment; increase of secretion after pilocarpin (about 30 gm. saliva). (4) After-period, in the third month after the treatment, 20 gm. saliva were again excreted after a pilocarpin injection. Serum had a weaker action than caseosan; venesection was just as effective. The experiments show that the above-mentioned procedures sensitize the autonomic system to stimuli, and the reactive action is of long duration; with adrenalin as long as a week, with pilocarpin as long as 2 weeks. The authors assume that these procedures produce products of catabolism which cause this alteration in the organism.

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**Nonspecific Stimulation Therapy. IV. Demonstration of the Atropin-Like Action of Human Blood.**

*H. Struck, Arch. f. exper. Path. u. Pharmacol., Leipsic, 93:140, May 2, 1922.*

Experiments were performed on frogs (*Rana temporaria*) whose  
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hearts were perfused with muscarin 1:40,000, which stopped heart action. In the detoxication experiments 0.5 c.c. of the muscarin solution was replaced by 0.5 c.c. atropin solution or atropin solution plus serum or plus serum extract. It was found that subthreshold doses of serum extract in 96% alcohol with atropin have a completely detoxicating action on the heart intoxicated with muscarin and the action of the serum extract is quantitatively equal to that of the serum from which it originated. The effectiveness of the serum increases with standing and its maximum of effectiveness is attained after 6 hours. Struck concludes that muscarin detoxication of the heart is caused by extractable substances of the serum which are soluble in alcohol. He found that these substances are preformed in the blood and do not develop from coagulation of the blood platelets. From the carotid of the rabbit or the ulnar vein of man blood was taken directly into alcohol, filtered, and dried at 50° C. The residue was again put in alcohol, evaporated at 50° C., and put in Ringer's solution. Results: in an experiment on himself the fresh blood extract was ineffective, but became strongly effective after a preliminary treatment of the donor with caseosan injected intramuscularly. Also the blood extract of other normal men or patients with certain diseases, including polycythemia, valve lesions, uric arthritis, cirrhosis of the liver and nephritis, was ineffective in 10 other patients with increased blood pressure, for example in cases of syphilis, pneumonia, endocarditis, tuberculosis and carcinoma; and in pregnant animals the serum and serum extract had an action similar to that of atropin on the heart intoxicated with muscarin.

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**The Essential Oils and Methods of Preserving Them.**

*S. Demiéville, Bull. d. sc. pharmacol., Paris, 29:311, June, 1922.*

The essential oils may be preserved by rigidly excluding the action of air and light, as by keeping in well-stoppered, brown or yellow bottles in a cool, dark place. However, these conditions are not always possible to observe. The oils may be satisfactorily preserved by adding perfectly pure alcohol, in proportions fixed for each oil. If not suitably preserved, the oils decompose and great variations result in the commercial products. For a large number of the oils, tabulated by the author, the suitable proportion consists of equal parts of the oil and 95° alcohol. For oil of anethum, 2 parts, for angelica seed, 9 parts, for green anise, 4 parts of 95° alcohol; for birch (buds), equal parts absolute alcohol; for German chamomile, 4 parts absolute alcohol are required. The oils tabulated include 85 of the commoner essential oils.

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**The Volatile Oil of *Mentha Aquatica* Linné, and a Note on the Occurrence of Pulegone.**

*Roland E. Kremers, J. Biol. Chem., 52:439, June, 1922.*

The oil of *Mentha aquatica* Linné distilled from normal mature plants, and grown with necessary cultural precautions, was found to consist largely of linalool acetate. Smaller quantities of another ester, of free linalool, of a free acid, and of a very unstable aldehyde were

also found to be present. The author remarks that the elaboration of the oil by the plant can be thought of as following the same course as that outlined for *Mentha spicata* Hudson but stopping with the esterification of linalool. The investigation confirmed the previous suggestion that pulegone is a constituent of the cohobated oil of peppermint.

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**A Historical and Pharmacodynamic Study of Mouse-Ear Hawkweed (*Hieracium Pilosella*).**

*H. Leclerc, Bull. d. sc. pharmacol., Paris, 29: 30, June, 1922.*

This composite plant grows in sandy places, on lawns, in the woods, and along the roads. In the Middle Ages the plant was supposed to cure hernia, dissolve calculi and produce other striking therapeutic effects. It has diuretic properties. It relieved a recent case of Bright's disease. In a case of gout, 20 drops of the fluid extract, given every 2 hours in water, produced marked diuresis. The fluid extract, 2 c.c. daily, was prescribed in a cardiorenal case with enormous dilatation of the heart, ascites, oliguria and edema of the legs; it gave great relief. The drug is also useful for promoting diuresis in grip. In a case accompanied by urinary excretion of 500 c.c., 4 gm. of the fluid extract in 36 hours was followed by increased diuresis and improvement. The infusion of the fresh plant is most effective. The entire plant may be chopped fine, placed in boiling water in 10% strength for half an hour, and 250 to 500 c.c. of the infusion given daily. Of the fluid extract, the daily dose is 2 to 5 c.c. For instance, 4 c.c. may be mixed with 100 c.c. lemon syrup and water, and taken as a tea at various intervals throughout the day. The drug is not toxic, does not injure digestion, and is a useful diuretic.

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**Bulbus Scillae.**

*Josef Markwalder, Schweiz. med. Wchnschr., Basel, 52: 560, June 1, 1922.*

The sea-onion is one of the oldest if not the oldest heart drug described in the history of medicine. Though not much used in Switzerland, squill preparations are extensively employed in England and America. F. Mendel is said to have been the first to reintroduce the use of squill systematically in heart treatment by giving the dry crude drug. But a fundamental requirement for a rational treatment is a definite quantitative determination of the effectiveness of the drug and its constituents. Of the qualitative composition of squill it is only known that it contains the heart glucosid, which is of special interest; sinistrin, traces of caffein, large amounts of mucus, abundant raphides, that is, large bundles of prismatic crystal needles of calcium oxalate, and a volatile stimulating substance. The chemical methods of determination have many disadvantages. At present the best method of qualitative determination is the physiologic determination of its effectiveness on living frogs. By the frog dose, FD, or titer value, is meant the absolute amount of active substance which is just fatal for 1 gm. of *rana temporaria*.

Author determined the effectiveness of the raw material of sea-onion with 8 million FD. Folio digitalis titrata has a titer-value of about 2 million FD. But there is a great discrepancy in clinical effectiveness as calculated in frog doses between digitalis preparations and squill; to obtain an equal effect it is necessary to use a much larger frog dose of squill than of digitalis. The effectiveness in warm-blooded animals of the pure substances of squill was tested by Hatcher's method. It took about twice the amount of squill to be as effective as a given amount of digitalis. Clinical experience, however, is decisive: standardization by frog doses has only a methodic value. Mendel emphasizes a specific action of squill on diastole. Author shows that squill causes an increase in amplitude of individual pulse curves parallel with an increase in general blood pressure, but no enlargement in the volume of the individual pulse beats.

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#### **The Pharmacology of Squill.**

*E. Jenny, Schweiz. med. Wchnschr., Basel, 52: 562, June 1, 1922.*

Author tested the action of squill on the frog's heart, with a view to answering the question of whether squill really does have an action similar to that of digitalis, and if so whether this action is identical with that of digitalis or whether differences can be demonstrated. For the experiments he used the preparation Scillaren. According to Straub's method of experiment the squill was tested on frogs' hearts filled with Ringer's solution, with Ringer's solution without calcium, and with Ringer's solution without potassium. With extraordinary frequency squill caused disturbances of conduction, between the sinus and ventricle as well as between the ventricle and auricle, which could be promptly overcome by small doses of potassium chlorid, larger doses of atropin or small doses of pilocarpin.

Squill has essentially the same action on the frog's heart as digitalis, but there are certain differences, which, however, are only quantitative. The action of squill is less lasting than that of digitalis; moreover, about twice as much squill as digitalis is necessary to produce the same effect. The great difference between squill and digitalis, with reference to the proportion between the toxic dose for the animal and the heart dose, indicates a different behavior of the two toxins with reference to resorption, changes in the organism and excretion. Loewy's assumption that the action of squill on the frog's heart is to be attributed to calcium sensitization is denied. But a pronounced difference between digitalis and squill could be demonstrated in another way, namely by the demonstration of their quantitatively and qualitatively different behavior, or of their colloido-chemical characteristics, especially with reference to blood. In a heart drug not only its action on the heart and vessel-wall is important, but also its action on the blood.

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#### **Studies on Strychnin.**

*Soma Weiss and Robert A. Hatcher, J. Pharmacol. & Exper. Ther., 19: 419, July, 1922.*

In the common grass frog, or leopard frog (*Rana Pipiens* Shreder),  
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a dose of crystalline strychnin sulphate (Merck's), equal to 0.15 mg. per kilo of weight, suffices to cause perceptibly increased reflex excitability after the animal has fasted until metabolism has become minimal. Frogs recently caught, and in which metabolism is active, require doses several times greater — relative to their weight — to induce increased reflex excitability. Tolerance toward strychnin diminishes gradually and apparently irregularly. Frogs which have fasted until their tolerance is minimal may have it increased by suitable feeding.

The liver of the frog is concerned in the destruction or elimination of strychnin when the poison is administered during a period of active metabolism, but not when it is administered during a period of minimal metabolism. The removal of the liver during this latter time has little influence, therefore, on the size of the dose required to induce increased reflex excitability. The removal of the liver during active metabolism causes an increase in its susceptibility toward small doses, so that the behavior is like that of a frog that has fasted for a long period, or until its metabolism is minimal. The frog having a minimal metabolism becomes apparently normal within a period of 48 hours after the injection of a dose of strychnin which is just sufficient to cause tetanus, so that no increased reflex excitability can be detected after the lapse of such a period. There is, however, a certain degree of latent persistent action, since such frogs exhibit an increased susceptibility toward strychnin for periods of several weeks after the administration of much smaller doses than those from which they apparently recover within 48 hours.

The Stas-Otto method for the extraction of poisons from animal tissues does not permit of the recovery of strychnin quantitatively when only very small amounts (but such as may be present exceptionally at the time of death) are present, but widely diffused in the organs. When one part of strychnin is present in ten million parts of tissue, it may be extracted almost quantitatively by liquefying the tissue by means of sodium hydrate and heat, and shaking the liquid with chloroform. When the blood of an adult human being contains as much as 0.5 mg. strychnin at the time of death, the poison probably can be detected by the means described. When the residue after the distillation of the chloroform is sufficient in amount to interfere with the absorbability of the poison from the lymph sac of the frog (or with the characteristic color reaction), this residue should be heated with concentrated sulphuric acid in order to destroy the organic matter other than strychnin, after which the residue is rendered alkaline and extracted by chloroform. Troublesome emulsions are sometimes formed, but the chloroform may be separated from such emulsions by shaking with chloroform or with water as circumstances require. Strychnin is lost during the process of extraction from tissues through adsorption by insoluble residues and by filter paper when in acid solution in water and in alcohol, but chloroformic solutions of the base may be filtered through small papers virtually without loss.

When 1 part of strychnin sulphate is added to 430,000 parts of a mixture of oxalated or citrated blood and an equal volume of normal salt solution, the strychnin is distributed between the corpuscles and the plasma nearly in proportion to their respective volumes. With increasing concentrations up to that of 1 part of the poison in 60,000



parts of diluted blood, the corpuscles fix increasing percentages of the strychnin, so that when this concentration is reached the corpuscles fix about 3 times as much as the plasma holds in proportion to their volume. When strychnin is added to blood in the higher concentration, fixation by the corpuscles appears to be maximum within 10 minutes. Erythrocytes fix approximately one-half of the strychnin sulphate which is added in the proportion of 1 to 20,000 parts of citrated blood and diluted with an equal volume of salt solution. Strychnin which has become fixed by the erythrocytes in this way is not removed when the corpuscles are washed repeatedly with citrated normal salt solution. When distilled water is added to the erythrocytes causing hemolysis, after they have fixed strychnin, the stroma retains the greater part of the poison.

Strychnin which has been fixed by the red corpuscles does not exert its typical action quantitatively so promptly after its intravenous injection into the cat as that which is held in solution in the plasma, and approximately 50% more of such absorbed strychnin is required to cause death promptly after its intravenous injection than of that which is held in the citrated plasma. Strychnin was injected intravenously into cats in doses of 1 mg. per kilo of weight, and after intervals of time, varying from 2 to 40 minutes, blood was withdrawn from the carotid artery in measured amounts, and the percentages of strychnin present in the corpuscles and plasma (or serum) were determined separately. Strychnin sulphate leaves the blood stream rapidly, and after 2 minutes as much as 30% may have left the circulation, within 5 minutes more than 50%, and after 40 minutes the blood may contain only about 4% of that injected.

Young animals appear to eliminate strychnin from the circulation more rapidly than adults. This probably stands in relation with the greater tolerance of young animals toward strychnin, but the difference in the rate of elimination found in these experiments is greater than the difference in tolerance of animals of the age used and that of adults. When strychnin sulphate is injected intravenously into the cat, the poison passes from the plasma into the tissues in part, in part into the corpuscles, and after a time it begins to pass from the corpuscles back into the plasma and thence into the tissues. In one experiment, after an interval of 40 minutes, the corpuscles were found to contain about 4% of the strychnin injected, while the plasma contained only traces, the concentration in the plasma being equal to 1 part in about 12,000,000. The distribution of strychnin between the plasma (or serum) and the corpuscles following its intravenous injection into the cat does not appear to differ materially from that seen when the poison is added to the blood in vitro in an approximately similar concentration. It is believed that the determination of the distribution of the poison between the plasma and the corpuscles will aid in the study of the behavior of strychnin in the body, and especially of its elimination, by means of perfusion experiments.

Strychnin sulphate was administered orally and intramuscularly in single doses of 4 mg. and in repeated oral doses. The urine was collected in periods of 6 hours, 12 hours and 24 hours, and the amounts of strychnin present were estimated by means of frog tests. The kidneys excrete amounts equal to 20% of that administered at one time, and a

much lower percentage of larger doses taken by the mouth over periods of 12 and 28 hours, respectively. The percentage of the strychnin excreted by the kidneys is a measure of the eliminative efficiency of the liver, rather than that of the kidney itself, for the kidney excretes only that which the liver fails to excrete. Diuresis hastens the elimination of strychnin by the kidney, but it does not necessarily increase the total amount eliminated in the urine after a single dose injected intramuscularly, and it may, in fact, be attended with the renal elimination of a smaller total than would occur in a similar experiment without diuresis. The liver appears to be the principal protective organ with reference to acute poisoning by strychnin, the kidney to be concerned mainly with the elimination of traces of the poison which reënter the circulation after having been fixed temporarily in those tissues which are incapable of destroying the poison.

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(1c—39)

(1c—39)

**Observations on the Amebicidal Action of Conessin.**

*H. C. Brown, Brit. M. J., London, p. 993, June 24, 1922.*

Conessin, an alkaloid having the formula  $C_{12}H_{20}N$ , has been isolated from several members of the family of Apocynaceae, and is here shown to exert a very strong inhibitory action upon the growth of free-living amebas; in fact exactly equal to that of emetin. Infusions of the seeds of these plants have for many years been used with marked success in cases of chronic dysentery. Although when administered subcutaneously conessin produces an area of necrosis at the site of inoculation, it can yet be administered by mouth or intravenously in suitable doses without producing symptoms. It is approximately 50% less toxic than emetin. A diminution of the inhibitory action on free-living amebas of solutions of emetin and conessin, which have been in contact with intestinal mucus, is shown. The serum of patients receiving full and repeated doses of emetin has apparently no amebicidal action; hence it is unlikely that the presence of conessin in blood-serum could be detected by its effect on amebas.

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(1c—40)

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**The Action of Different Groups of Local Anesthetics in the Light of Different Methods of Examination.**

*Konrad Fromherz, Arch. f. exper. Path. u. Pharmacol., Leipzig, 93: 34, May 2, 1922.*

For the purpose of testing local anesthetics as to their availability as conduction or surface anesthetics, the objects used were the cornea of the rabbit; the skin of the reflex frog, where only the abolition of the reaction to acids was considered; and the sciatic nerve of the rabbit, the nerve being exposed and wrapped in a tampon with the solution to be tested.

The substances tested were (1) Carbonic acid ester: (a) phenol-carbonic acid ester; (b) p-aminophenolcarbonic acid ester; and (c) v-m-xylencarbonic acid ester. Injected intravenously they are toxic. Symptoms of phenol intoxication develop, but in 2 or 3 minutes the animals revive. On account of their ready cleavage, they are poor

superficial but good conduction anesthetics. The xylene esters in solid form are more stable and can be preserved better and therefore they are more effective even on the frog's skin than the other esters. On account of the readiness with which they are decomposed these substances have no practical importance. (2) Aromatic alcohols: (a) phenylcarbonic acid ester; (b) p-aminophenylcarbonic acid ester; (c) carbo-ethyl-p-aminophenylcarbonic acid ester; and (d) phenylethyl alcohol. The toxic action is the same as in Group 1 except that there are not signs of irritation, but of narcosis. For conduction anesthesia they are as strong as novocain, for superficial anesthesia they are superior to Group 1 and novocain. Yet these preparations cannot be used because they are only slightly soluble and have an irritant action on tissues (conjunctivitis, inflammation at the point of injection). (3) Novocain and cocain: Novocain is inferior to cocain as a surface anesthetic, but on account of its ready solubility and the reversibility of the interruption of conduction, it is superior to the latter as a conduction anesthetic, particularly in combination with adrenalin, as the adrenalin prevents the resorption of the store of novocain. (4) Benzoyl- $\beta$ -oxy- $\alpha$ -diethylamino-ethylbutyric acid ester: The action of this preparation is closely related to that of cocain. Subcutaneously it is surer to be resorbed than cocain, but its action is not more intense than that of the latter drug; when injected intravenously, however, it is 3 times as toxic as cocain. The new preparation dilates the vessels and therefore 3 times as much adrenalin must be added as to cocain. It is very much superior to cocain, both in its action on mucous membranes and on nerve trunks (5) Eucupin-vuzin: Vuzin has the maximum anesthetic action of this series. The slow beginning of its action and the long persistence of the anesthesia are characteristic.

*General Conclusions.*—Substances which are readily diffusible and readily resorbable, such as novocain, carbonic acid ester and aromatic alcohols, can be used as conduction anesthetics. In the case of the carbonic acid esters their easy cleavage interferes with their effectiveness. On the other hand substances that are only absorbable with difficulty, such as cocain, oxybutyric acid and vuzin, when given subcutaneously are not very violent in their action and are suitable for surface anesthetics; but given intravenously their action is rather severe. In general it may be said that preparations which on account of their relative mildness of action, ready diffusion and cleavage, are not effective on mucous membranes, have a good action on nerve trunks or in infiltration anesthesia and are to be recommended as conduction anesthetics. On the other hand, preparations of slight resorbability and adsorbability by the tissue colloids only enter the circulation slowly from the mucous membranes and therefore, in spite of the intensity of their action, they do not produce any general symptoms and are good surface anesthetics.

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(1c—41)

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**The Rôle of Hexamethylenamina in the Production of Hematuria.**

*W. A. Bloedorn and J. E. Houghton, J. Lab. & Clin. Med., 7: 514, June, 1922.*

During the epidemic of influenza in the winter of 1920-21, 400 of  
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the milder cases at the Naval Academy were treated routinely with a solution of brown mixture and hexamethylenamin. Of the 400 patients 4 developed a sudden, apparently inexplicable, hematuria. In a fifth case outside of the naval reservation hematuria developed following the administration of the same drugs. The time elapsing between the beginning of medication and the appearance of hematuria varied from 1 to 7 days, the average daily dose of hexamethylenamin being 30-40 gr. in brown mixture as the vehicle.

An attempt was made to ascertain the factors or possible predisposing causes concerned in the production of the hematuria. Attention was first directed to the action of the urine in view of the recognized fact that hexamethylenamin must have an acid medium in order to liberate the formaldehyd on which its antiseptic action depends. In all the cases there was high total acidity and high H-ion concentration of the urine. In order to establish the rôle of urinary acidity in the production of hematuria, hexamethylenamin was administered to 4 control subjects whose urine showed a high acidity. None of these developed hematuria even after 8 consecutive days of drug ingestion. The acidity of the urine was decreased in all 4 cases upon completion of the experiment. A second experiment was conducted with 4 persons in whom the urinary acidity had been increased by the addition of acid sodium phosphate. No hematuria developed in any of these after a period of 8 days.

In all the experimental subjects the constant liberation of formaldehyd was indicated by a positive Burnam test, which is obtained within  $\frac{1}{3}$  to 3 hours after the drug is taken, provided the urine is sufficiently acid. A third experiment was carried out on 4 selected persons whose urine was rendered less acid by addition of sodium bicarbonate. The combined doses were 1 gm. hexamethylenamin and 2.5 gm. of sodium bicarbonate, 4 times daily for 8 days. The sodium bicarbonate was sufficient to prevent the liberation of formaldehyd in the urine in almost every instance.

The fact that formaldehyd is liberated only in the presence of an acid urine suggests high urinary acidity as an important, but not the sole, factor in the production of the hematuria. It is believed that drug idiosyncrasy was the essential element in this complication. A skin test with various dilutions of the drug was employed to demonstrate an idiosyncrasy. All 5 of the patients showed positive skin tests, the size of the zone of reaction being proportional to the severity of the hematuria. In 12 controls the test resulted negatively. The controls had received hexamethylenamin for 8 days previously without untoward effect. Aside from dilute formalin (1:50), none of the control solutions (caffein 1:10, salicylic acid 1:10, quinin chlorhydrosulphate 1:20, adrenalin 1:1000, normal saline) produced the characteristic redness and induration at the site of inoculation. The formalin had a slight local, irritative, nonspecific effect.

There is fairly conclusive evidence that there was a specific susceptibility and hypersensitiveness to hexamethylenamin, which would indicate that the allergy is the causative factor in the production of hematuria. The symptoms (tenesmus, vesical pain, marked irritation and terminal hematuria) point to the bladder as the seat of the hemorrhage. Absence of constitutional symptoms and lack of urinary findings, such as blood casts, tend to rule out acute hemorrhagic nephritis. Cysto-

scopic examination revealed hemorrhagic bladder lesions sufficient to account for the symptoms.

In an attempt to reproduce the symptoms and lesions in guinea-pigs, a daily dose of 20 mg. produced hematuria in 2-7 days. The widespread lesions indicated marked toxicity of the drug for these animals. In the guinea-pig the kidneys are the main source of the hematuria. It is barely possible that a similar renal condition could be produced in man if the drug were given in enormous doses over a sufficient length of time.

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(1c—42)

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**A New Antiseptic with High Iodin Content (Diethylendisulphid Tetra-Iodid).**

*C. Bachem, Biochem. Ztschr., Berlin, 129:190, April 19, 1922.*

Diethylendisulphid tetra-iodid is a new organic preparation with very high iodine content and highly antiseptic properties. It is a bluish-black powder having a strong, penetrating odor recalling partly garlic and partly mercaptan. Besides 10% sulphur it contains 80.89% iodine in the molecule. The substance was tested for cleavage of iodine in water and albumin solutions for the action of diffuse sunlight and daylight and its germicidal and toxic action determined. Its antiseptic power is exceptional, the toxicity not too high and in its practical application it should be equal to other iodoform substitutes that split off iodine easily. The penetrating odor, that cannot be suppressed even by bolus trituration, as well as an irritative action on the mucosa are drawbacks. As the preparation also contains sulphur it is applicable to parasitic cutaneous diseases when the joint action of iodine and sulphur is desired.

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(1c—43)

(1c—43)

**The Hemolytic Properties of Arsphenamin and 15 Allied Compounds.**

*G. P. Grabfield, J. Pharmacol. & Exper. Ther., 19:343, June, 1922.*

Using sheep's red corpuscles as a test object, the hemolytic activity of various samples of arsphenamin was found to vary in a general way as did the toxicity, when the latter depended upon variations in the conditions of the reduction of the nitro-group to the amino-group in the preparation of the sample. On standing or after shaking in alkaline solution, the hemolytic properties of a given sample decreased, often disappearing altogether. Arsonoxid was nonhemolytic. The sodium salts of various substituted phenylarsonic acids related to arsphenamin were nonhemolytic. Warming a sample of disodium arsphenamin to 55° C. decreased its hemolytic power. Warming the hydrochlorid caused comparatively little diminution of hemolytic power when tested after being changed to the disodium salt. The hemolytic power of dihydroxyarsenobenzene (in 1% solution of sodium salt) was nil, but the introduction of amino-groups caused the resulting compounds to acquire hemolytic properties in direct proportion to the number of amino-groups introduced. The antihemolytic action of arsphenamin was similar to that described for sodium arsenate and arsenite when tested against chemical hemolytic agents. None of these substances exerted an antihemolytic action against rabbit hemolysin. The presence of serum inhibited hemolysis by arsphenamin.



(1c—44)

(1c—44)

**Propyl and Isopropyl Mercury.**

*M. Goret, Bull. d. sc. pharmacol., Paris, 29: 297, June, 1922.*

For preparing dipropyl mercury, sodium amalgam reacts with propyl iodid or bromid, a little acetic ether being present as catalyzer. In a strong flask capable of being agitated 2 kg. of 7:1000 sodium amalgam is placed, and about 120 gm. (slight excess) propyl bromid is added either all at once or in several portions, followed by 12 gm. acetic ether, after which the mixture is agitated. In 15-20 minutes, the action becomes vigorous, with rise of temperature. The agitation is stopped if necessary, but resumed at intervals until the reaction is complete, which occurs in 5 or 6 hours. About 150 gm. water is then added, the mixture is agitated quickly for several minutes and then distilled with steam. The dipropyl mercury passes over. The supernatant liquid and denser oil are decanted, mixed, dried over  $\text{CaCl}_2$ , and distilled at ordinary pressure. A small quantity of bromid of propyl mercury present separates on cooling. Crystallization in alcohol yields a substance melting at  $135^\circ\text{C}$ . and appearing as brilliant scales. In rectifying 170 gm., 30 gm. pass at  $179^\circ$  to  $185^\circ$ , 55 gm. at  $185^\circ$  to  $188^\circ$ , and 68 gm. at  $188^\circ$  to  $191^\circ$ . The substance passes chiefly at  $189^\circ$ . An unknown impurity is present with the portions passing between  $185^\circ$  and  $188^\circ$ .

Dipropyl mercury, or mercuric propid, is a clear, colorless and highly refractive liquid, of 2.046 sp. gr. It has a strong characteristic odor. Its taste, at first flat like vaselin, becomes metallic and disagreeable. In vacuo, and under 25 mm. pressure, it distils at  $82$  to  $86^\circ\text{C}$ . At ordinary pressure, its boiling point is  $189^\circ\text{C}$ . If more than 100 to 200 gm. be distilled at a time, decomposition is likely to occur. The substance is insoluble in water. In  $90^\circ$  alcohol, it dissolves in 3 times its volume at boiling point, and in about 12 volumes at  $20^\circ$ . In ether, it dissolves in equal volume around  $36^\circ$ , and in 12 volumes at  $12^\circ$ . The halogen salts and acetate may be prepared with mercuric chlorid, bromin or mercuric bromid, iodin, and hot or glacial acetic acid.

For preparing diisopropyl mercury, 2720 gm. 7% sodium amalgam is placed in a strong flask, and 123 gm. isopropyl bromid is added in several portions, with 13 gm. well dried acetic ether. The mixture is agitated for 15 minutes and then becomes hot. The reaction is at its maximum in about 2 hours, when agitation should be stopped. The agitation is resumed as each new portion of isopropyl bromid is added. In about 10 hours, 100 c.c. water may be added, and the mixture distilled with steam. The distillate is dried over  $\text{CaCl}_2$  and redistilled. The acetic ether and excess bromid are separated at ordinary pressure. At about  $85^\circ\text{C}$ , the liquid becomes turbid on account of liberated metallic mercury. The product is then placed in a small flask and the rectification finished in vacuo. Under pressure of 25 mm., the product distils almost completely at  $75$  to  $77^\circ\text{C}$ . Only 8-10% of the theoretic yield is obtained by this process.

Diisopropyl mercury is a clear, colorless, strongly refractive and heavy liquid, of 2.050 sp. gr. at  $0^\circ\text{C}$ . Halogen compounds are formed by employing halogen salts of mercury. Nitric acid produces at first a mixed salt, then, if heating is continued, mercuric nitrate. Alcoholic solution of silver nitrate reduces the compound, liberating metallic mercury. The hydrate may be prepared with moist silver oxid.

(1c—45)

(1c—45)

**Physiopathology of the Hematopoietic Lymphatic System after Injection of Various Dyes.**

*Antonio Ciminata, Policlinico (Med. Sect.), Rome, 29: 319, June 1, 1922.*

The author endeavored to ascertain the behavior of the hematopoietic lymphatic system in animals following injection of various dyes, by poisoning the animal and investigating the actual disposition of the colored material in the various organs and tissues injured by the poisons administered, as well as in other organs not entirely acted upon by the toxic agents.

Experiments were conducted on 17 rabbits and 2 guinea-pigs. All of these animals received, for various lengths of time and either by the subcutaneous or intravenous route, or by both at once, injections of a solution containing 5% carmin in lithium carbonate; these animals were subsequently killed by the administration of various kidney poisons—mercuric bichlorid, arsenic, cantharides, pilocarpin, uranium nitrate or uranium acetate. In each case the findings were the same: no gross lesions of the hematopoietic lymphatic apparatus, except for a more or less deeply reddish coloration of lymph glands.

Histologic examination of individual organs reveals deposition of carmin, principally in the lymph glands and bone-marrow; scant deposits in the spleen, occasionally none at all. There were no deposits of carmin in the bone cells nor in the Haversian canals.

Carmin was found deposited in the connective tissues (reticular elements, endothelium of blood and lymph vessels, perithelium); the dye was not phagocytized by macroblasts or microblasts or by the cells of the splenic pulp, nor was it deposited in the specific functional cells of the various organs of the blood-forming apparatus. The spleen represents a depository of negligible importance as far as carmin is concerned. The various toxic substances administered did not produce histologic changes discernible by the common methods of examination either in the bone-marrow, lymph glands, or spleen.

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(1c—46)

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**An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test.**

*S. M. Rosenthal, J. Pharmacol. & Exper. Ther., 19: 385, June, 1922.*

Phenoltetrachlorphthalein was injected intravenously and its consequent concentration in the blood studied. In normal dogs there was an immediate rise to approximately 10%, rapidly falling to only a trace or to complete disappearance within 15 minutes. When the liver was damaged, the amount of dye in the blood reached 15 or 30%, and remained elevated for a prolonged period, 11% having been recovered almost 2 hours after injection. There was evidence that the curves obtained paralleled the degree of impairment of liver function. It is believed that the method can be applied clinically as a quantitative test for liver function.

(1c—47)

(1c—47)

**The Absorption of Mercury Bichlorid and Trypaflavin by Bacteria and Body Cells.**

*M. Hahn and E. Remy, Deutsch. med. Wchnschr., Leipsic, 48: 793, June 16, 1922.*

The author tried to determine to what extent the body cells in contrast with the bacteria observed chemical substances from a solution of a given concentration, and in this way to find out whether it is possible to introduce just the right amount of a substance into the circulation so that no injury of the body cells may be produced but that the bacteria may be killed or inhibited in development. The drugs used were bichlorid of mercury and trypaflavin and they were tested on guinea-pigs' livers and *Bacillus coli*. Results showed: (1) A liver preparation or colon bacilli brought into contact with trypaflavin or bichlorid solution at 37° C. and shaken, caused a pronounced decrease in the concentration of the solution which was visible colorimetrically and chemically. (2) On an average 100 gm. damp colon bacilli substance took up 2.6 gm. trypaflavin and 11.65 gm. bichlorid; 100 gm. moist liver preparation, only 1.37 gm. trypaflavin and 8.34 gm. bichlorid. (3) The absorption by the body cells was less when the disinfectants were dissolved in cattle serum, which considerably decreased the adsorption for both kinds of cells. (4) Even on calculating for dry substance these differences are clearly perceptible. (5) The same results were obtained in an experiment in which the liver was perfused with trypaflavin solution (serum or Ringer's).

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(1c—48)

(1c—48)

**Poisoning by Butter of Antimony.**

*William Bell, Brit. M. J., London, p. 917, June 10, 1922.*

Commercial antimony chlorid, commonly called butter antimony, contains an excess of acid which gives it a power of corrosion in addition to that effected by the antimony ions which are readily separated.

A farmer, aged 46, was found early in the morning lying in a stream, conscious. He was assisted home and put to bed. Skin was cold and livid, pulse rapid and full. He had vomited, and attempts to swallow warm milk were followed by violent retching. Near the stream was found a bottle labelled "Butter of Antimony," which the patient had purchased for treating a horse's foot. He became worse, with burning pain in the stomach and died 8 hours after swallowing the poison. On opening the abdomen, the stomach bulged forward, deep red in color; a few coils of small intestine were red on the anterior surfaces. There was a red stain on the great omentum adjoining the greater curvature, and another at the duodenal junction. The whole outer surface of the stomach was plum red. The contents were 20 oz. of dark, almost black, fluid. After being washed the inner surface was black. The mucous coat had been transformed by charring into friable material, and its surface shed. It appeared that not more than 6 dr. of poison had been taken; recoveries of 4-5 dr. have been recorded. In this case the stomach was vulnerable, being empty at the time of administration; subsequent ill effects were intensified by the patient lying in a cold stream. By the drinking of water to slake the burning the strong

irritant was rapidly diffused over the interior surface of the stomach and free acid liberated.

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(1c—49)

(1c—49)

**Studies of Chronic Intoxications in Albino Rats. VI. Lead Carbonate.**

*Rorald Sollmann, J. Pharmacol. & Exper. Ther., 19:375, June, 1922.*

Rats to whose food lead carbonate was added in small doses (daily 0.0007-0.15 mg. per kilo) showed a slight but definite check of growth and appetite. The effect started within 8 weeks and increased with the duration of the feeding. No other definite symptoms occurred, even when the administration of lead extended over 35 weeks. The mortality was rather high, between 9 and 17 weeks, due probably to lowered resistance. Another group of rats grew and ate normally although fed on larger doses of lead (0.3-1.22 mg. per kilogram per day for 8 weeks). These animals were younger, which may possibly account for their resistance. The daily dosage of lead in human plumbism probably begins with  $\frac{1}{5}$ - $\frac{1}{3}$  gr., 0.2-0.3 mg. per kilogram. It is seen that much smaller doses, corresponding to as little as 1/1500 gr. per man per day, are not harmless to rats. It is improbable that rats are much more susceptible to lead than is man. It is much more probable that these minute doses would also interfere with the nutrition and resistance of man, although they do not produce the clinical picture of plumbism. The results tend to throw some light on the wide hiatus that probably exists between clinical disease and harmlessness.

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(1c—50)

(1c—50)

**Biochemic Studies in a Fatal Case of Methyl Alcohol Poisoning.**

*I. M. Rabinovitch, Arch. Int. Med., 29:821, June 15, 1922.*

The uric acid content increased from 3.1-9.3 mg. per 100 c.c. in less than 6 days. The urea nitrogen content increased from 42-144 mg. per 100 c.c., and the creatinin content from 1.6-4.5 mg. per 100 c.c. blood in the same period. The acid soluble phosphorus varied from 8-11 mg. per 100 c.c. blood calculated as phosphorous. The initial high findings may have been due to a previous chronic nephritis. There can be no doubt, however, that the rapid changes noted daily were due to the action of the poison. Such findings suggest a complete renal block, and correspond to those occasionally found in the acute retention in hypertrophy of the prostate, or the anuria of mercuric chlorid poisoning. That the kidney function was practically nil was also supported by the rapid increase in the uric acid and creatinin content of the blood. The patient took no food during the few days of illness. It may therefore be assumed that all the uric acid found was of an endogenous origin. The anatomic findings appeared to corroborate this view. Hyperglycemia was present throughout the course of the disease. The lowest concentration of sugar, found at the first examination, was 0.182%. This gradually increased to 0.228%. The impairment in the kidney function seems sufficient to account for the hyperglycemia. The plasma carbon dioxid combining power on admission was 46

volumes per cent.; it eventually fell to 26 volumes per cent. The retention of phosphates in the blood would explain part of the acidosis. It does not appear unreasonable, on theoretical grounds, to suggest that the acidosis may have been due partly to the formation in the body of methylene derivatives, from the action of the formaldehyde on the amino-acids present. Cyanosis was very slight at first, but became more marked during the progress of the disease. At the first examination the oxygen unsaturation was 9 volumes per cent. Assuming that arterial unsaturation may have existed, its cause under the circumstances (poisoning) was problematic. No gross changes occurred in the respiratory or circulatory systems. During the first examination of the blood for methemoglobin, none could be found. The cyanosis gradually became more marked, and on the following day a definite bronchopneumonia was found clinically. The blood examination one-half hour before death, at which time there was a very marked degree of cyanosis, also did not show the presence of methemoglobin. At this time the oxygen capacity was practically normal. It may therefore be assumed that either no methemoglobin was formed, or that it was eliminated as rapidly as it was formed, and played no important part in the production of the cyanosis. Methyl alcohol could be detected in the tissues 6 days after the ingestion of the drug.

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(1c—51)

**Nitrous Acid Poisoning.**

*W. St. Clair McClure and Harri Heap, Lancet, London, 202: 1142, June 10, 1922.*

A family of 6 persons, ranging in age from 8 to 38 years, were poisoned by the accidental contamination of food with a powder thought to be table salt. A dog and a cat also ate some of the food. The symptoms consisted of dizziness, a feeling of suffocation and nausea between 15 and 20 minutes after ingestion of the food. Some of the patients vomited and had severe abdominal pain. The children became blue and almost unconscious within  $\frac{1}{2}$  hour. There was no diarrhea. Recovery took place in from 2 to 5 days, but 2 weeks later the mother and 2 of the children still had weakness of the legs. The cat died in 15 minutes, and the blood showed absorption spectra given by nitric oxid hemoglobin. The amount of the substance consumed by each individual was estimated and it was found that the severity of the symptoms depended on the relation between the amount of the substance ingested and the body weight. Specimens of the food and of the stomach contents of the cat were found to contain sodium nitrite.

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(1c—52)

**Carbonic Oxid in Tobacco Smoke.**

*Henry E. Armstrong, Brit. M. J., London, p. 992, June 24, 1922.*

Sulphuretted hydrogen and prussic acid in minute proportions are constant products of smoking. Smoking a cigarette, pipe or cigar by attaching it to a gas-sampling bottle, and allowing mercury to run out in "puffs", shows that 80% of air in excess was drawn through the cigarette, only 50% through the pipe, under 30% through the cigar.

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In the latter, both the amount and high ratio of carbon monoxid to dioxid are remarkable  $\left( \frac{13.36}{5.8} = 2.3\% \right)$ . To ascertain the effect of smoking more or less rapidly, the rate at which mercury was released was varied. The proportion of carbonic oxid in the smoke varies according to the rate of smoking. When air is drawn in rapidly, the length and temperature of the glowing portion are increased, and more monoxid is formed. A normal sample of cigarette smoke contains between 0.5 and 1% carbon monoxid. In these trials the smoking was artificial; in a final series, cigars were smoked in the usual manner; smoke drawn into the mouth was afterward expelled into a mercury receiver and then analysed. Apparently results are little affected by make or quality; closeness of packing and rate of smoking seem the determining factors. Comparison of the proportions of carbonic oxid in straight coal gas (made by simply distilling coal) with that in tobacco smoke showed that in 1 cigar 0.303 cu. ft. of smoke was produced, of which 7% was carbonic oxid; the quantity of coal gas containing an equivalent amount of carbonic oxid is 0.25 cu. ft. The blood of the cigarette smoker often shows signs of carbonic oxid absorption. There is room for further study of the conditions regulating the natural exchange of carbonic oxid for oxygen in the blood.

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(1c—53)

(1c—53)

**Carbon Monoxid Poisoning Followed by Gangrene and Rectovesical Retention.**

*Alban Girault and André Richard, Presse méd., Paris, 30:556, July 1, 1922.*

A woman, 37 years old, was poisoned by carbon monoxid gas on November 20 and remained semiunconscious for four days. At the end of that time she had eschars over various parts of the body. When she entered the hospital on November 29, the bladder was found enormously distended, but retention of urine developed only nine days after the intoxication and was associated with retention of feces. Lumbar puncture on December 16 revealed the presence of a slight lymphocytosis. The spinal fluid was normal again on January 21. The patient began to regain control of her bladder on December 3. A slight quantity of albumin was found in the urine on December 10 only, but a phenolphthalein test three months later gave an abnormally low figure (27%). It is suggested that hematomyelia of the medullary cone may account for the symptoms observed in this case.

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(1c—54)

(1c—54)

**Histologic Study of Chronic and Acute Benzol Intoxication.**

*G. Brandino, Riforma med., Naples, 38:507, May 29, 1922.*

Benzol is a powerful leukotoxin; it destroys the parenchymatous cells of the hematopoietic organs. The most seriously injured tissue is the myeloid. This and the lymphadenoid tissue become aplastic after a series of 15 to 16 injections, but if the action of the benzol be suspended, complete regeneration ensues. The elements which best resist

are the small lymphocytes and the polyblasts which are still present in the medulla after all the other cells have disappeared and it is evident that these small lymphocytes have an important action in the regenerative processes, such as their transformation into large lymphocytes and the successive transformation of these latter into granulocytes, erythroblasts and megakaryocytes. In the advanced stages of regeneration the spleen presents myeloid cells of every type; the low percentage of normoblasts and myelocytes in the blood might be regarded as indicative of an autochthonous origin of the myeloid tissue in the spleen.

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## 1d. BACTERIOLOGY AND PARASITOLOGY

(1d—57)

(1d—57)

### **A Method of Successive Staining for Bacteriologic Purposes.**

*R. Monimart, Bull. d. sc. pharmacol., Paris, 29: 305, June, 1922.*

This method, applicable to the same slide, was devised for use in cases where few slides are available for examination. The slide is dried and fixed carefully. It is exposed for a few seconds above the hood of a Bunsen burner to a temperature of about 40° C., cooled, and examined by oil immersion.

The oil is removed with xylol, the preparation decolorized with one-third nitric acid for a minute, freely washed and drained, and Gram stained with phenol gentian violet, left for 2 minutes, cold. The slide is drained, but not washed, and stained for 3 minutes with Lugol's solution; drained without washing, exposed to absolute alcohol for 15 minutes, or to alcohol-acetone for 5 minutes; washed, stained with dilute fuchsin for a second, washed, drained, dried and examined.

If the preparation contains gonococci, the Gram stain with acetic neutral-red should be used for restaining.

The slide is again decolorized and the Ziehl-Nelsen fuchsin stain is applied. The slide is decolorized with one-third nitric acid, treated with 90° alcohol, rapidly washed, stained with methylene-blue, washed, dried and examined without cover-glass. During heating with the carbol fuchsin, small bits of blotting paper, or filter paper, placed on the slide, prevent rapid evaporation of the stain.

For preservation, the slide is decolorized for a few minutes with one-third nitric acid, then impregnated with silver by Tribondeau's method, as described in 1917. Blood-stained with the Romanowsky, bieosinate or Giemsa stains may be decolorized and treated with the Ziehl stain to show acid-fast bacilli, or with Tribondeau's silver method to show treponema.

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(1d—58)

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### **What Are the Atmospheric Moisture Requirements of Bacteria.**

*Nicholas Kopeloff and Sterne Morse, J. Lab. & Clin. Med., 7: 555, June, 1922.*

For these experiments it was found simple, economical and efficient to use sterile Petri dishes. Two tops or 2 bottoms are joined edge to edge and sealed with adhesive tape ( $\frac{1}{4}$  in.) around the equator. Agar

to support the growing culture is placed in the upper dish and solutions of dehydrating agents of varying concentrations, yielding a definite vapor tension and relative humidity, are placed in the lower dish. On the hardened agar surface is deposited 0.1 c.c. of a suspension of the organism to be studied. *B. coli*, *Staphylococcus aureus* and *B. subtilis* were subjected to the tests. A surface growth is obtained since variations of growth in the depth of the media are more difficult to measure and control. The plate is then inverted and 35 c.c. of solution of known concentration of glycerin calcium chlorid or sulphuric acid are added to the other dish. The 2 dishes are tightly bound together with adhesive tape and incubated at 37.5° C. for 18 hours.

Saturated calcium chlorid (B. P. 132° C.) with and without an equal volume of water was compared with water as a control; likewise glycerin (sp. gr. 1.258 at 20° C. B. P. 157° C. under pressure of 205 mm.) in the same proportion. Maximum growth was obtained in a humid atmosphere (i. e., where water was present). The minimum growth was obtained in the least humid atmosphere (i. e. where the concentrated calcium chlorid, yielding a relative humidity of 35-48%, and glycerin, yielding a relative humidity of 0-55%, acted as strong dehydrating agents). The solutions of half strength occupy an intermediate position (yielding relative humidities of 75-85%). Striking differences in colony formation were also noted. On the plates where a dry atmosphere obtained, the colonies were much smaller, with very irregular outline and surface.

By maintaining an incubator at a relative humidity of 10-40% (at 37.5° C.) it was found that the above results with the solutions were practically duplicated. It is essential therefore to keep sufficient moisture in the atmosphere of the ordinary bacteriologic incubator to develop characteristic colony formation.

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(1d—59)

(1d—59)

**Löhner's Marginal Ridge at the Germ-Free Area as a Support for Arndt's Fundamental Law.**

*W. Seifert, Biochem. Ztschr., Berlin, 129: 50, April 19, 1922.*

Löhner carried out experiments on growth promotion in the so-called oligodynamic metallic action by allowing agar plates with cast-in silver coins to stand 12 hours in an ice-chest and then inoculating them with bacteria. A sharply demarcated germ-free area showed itself around the coin while good bacterial growth had taken place on the remaining parts of the plate. At the border between both regions there then formed, in Löhner's experiments, a zone of specially profuse bacterial growth that became more and more pronounced in course of time. The marginal ridge produced at the destructive zone's border is said to arise from the growth-promoting stimulus of the silver concentration that prevails there.

Accordingly Löhner's plate experiment would constitute a special case of Arndt's fundamental biologic law, which states that substances destructive to protoplasm in strong concentration, and injurious to the same in weak concentration, are capable in still weaker concentration of stimulating the vital phenomenon until, finally, in strongest dilution they become indifferent. This conception is supported by Cobet and

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van der Reis. In contradistinction thereto Löhner, Friedberger and Süpfle maintain that a growth-increasing effect of oligodynamic influences is involved. Experiments were therefore undertaken in this direction which confirmed the fact that a marginal ridge may be formed as a result of favorable nutrient material alone. In the formation of the oligodynamic marginal ridge, however, experimentally demonstrable direct relations with the oligodynamically active substances play the determining part. The conception of the oligodynamic marginal ridge as a special case of Arndt's fundamental law, which was rejected by Löhner's, is consequently justified. The theoretic views developed by Cobet and van der Reis on the diffusion processes in the nutrient medium do not, however, take sufficiently into account the complicated character of the actual conditions.

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(1d—60)

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**The Influence of Arsenous Acid on Bacterial Growth (with Remarks on Formation of Marginal Ridges by So-Called Oligodynamic Metallic Action).**

*R. Cobet and V. van der Reis, Biochem. Ztschr., Berlin, 129:73, April 19, 1922.*

The question whether arsenous acid in smallest doses is in general capable of exerting a growth-promoting stimulus on young cells in course of development was investigated on bacteria in order to exclude individual differences. The dosage of the chemical stimulus presented difficulties. *Bacillus prodigiosus* plates showed a gradual fading of the injurious arsenical action up to indifference without the interposition of a growth-promoting zone. The promotion of growth may be explained by the more abundant supply of nutrient material. In general the experiments showed that when arsenous acid diffuses from a central depot into an agar plate a germ-free region and, under definite conditions, an adjacent marginal ridge of specially profuse bacterial growth was produced. This, however, is not the effect of a definite toxic concentration but is produced also by favorable nutrient material. The same applies to the marginal ridges that are found around silver coins as a result of the so-called oligodynamic metallic action. Promotion of bacterial growth by arsenous acid could not be demonstrated.

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(1d—61)

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**The Effect of Slight Increase of Temperature on the Bacteriostatic Power of Gentian Violet.**

*John W. Churchman, Bull. Johns Hopkins Hosp., 33:227, June, 1922.*

Continuing his researches upon the value of gentian violet as a bactericidal agent, Churchman has found that the power of this dye to inhibit the growth of *Bacillus coli* on plain agar is very greatly increased by using the dye heated to a moderate degree. Bacteria which will withstand the dye for an hour at room temperature are promptly inhibited if the dye is heated to a temperature of 50° C.; sometimes even 30° C. will inhibit growth. Neither heating of the organisms alone, without use of the dye, nor exposure to dye without

heating will inhibit growth. Again, exposure first to 50° C. and subsequently to unheated dye, does not inhibit. The 2 factors must be applied simultaneously. The cause of the increase of bactericidal power of the dye when moderately heated remains unknown. The lesson is that in using gentian violet and other anilin dyes for clearing up infections clinically—joint infections, sinous trouble, empyema, etc.—the dyes should be applied hot to get the best results.

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(1d—62)

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**Studies in Postmortem Bacteriology: Value and Importance of Cultures Made Postmortem.**

*Alfred S. Giordano and Arlie R. Barnes, J. Lab. & Clin. Med., 7: 538, June, 1922.*

This investigation was made for the purpose of determining 2 questions: Does invasion occur postmortem, and, if so, within what limits? Do bacteria recovered at postmortem have any intravital significance?

The following technic which was adopted, should be carried out with scrupulous attention to details. The organ to be cultured, free from adjacent tissue fluids and melted fat, is seared with a red-hot spatula. A sterile 5 c.c. pipette is thrust through the seared surface to the depth of the organ and material removed for culture. Rosenow glucose-brain broth tubes are immediately inoculated with this material. With this culture method it is possible to grow both aërobic and anaërobic organisms because of its graded oxygen tension. Blood agar plates are inoculated and smears for microscopic examination are prepared with the same material. The blood and spleen of 213 cases were so cultured routinely. Other systems, such as genito-urinary, respiratory and cerebrospinal, were cultured as conditions demanded. The pathogenicity of the organisms recovered in obscure cases was determined by animal inoculation, rabbits or other laboratory animals being used.

In a general way the reliability of postmortem cultures was estimated by comparison with antemortem cultures on the same case. Of 22 cases studied with this in mind, in 15 the results were in agreement. The cases which were not in agreement may be explained by the fact that antemortem cultures may have been made several days before death, prior to the advent of an infectious process, or they may have been attempted in a period of bacteremia which later disappeared. Discrepancies between antemortem and postmortem cultures need not necessarily be attributed to agonal or postmortem invaders. As shown in this series of cases, the so-called terminal infection may in reality be the immediate cause of death. Reliability of results may be established by a study of the fatal noninfectious cases, such as brain tumor, cerebral hemorrhage, and exophthalmic goiter. Of 40 cases so classified postmortem cultures were negative in 39 instances. These cultures were made from 1-23 hours after death. Apparently invasion of the blood by flora of the intact intestinal tract seldom occurs within this time limit.

In an unexplained and apparently unrelated series of fatalities not diagnosed clinically or pathologically, investigation showed these deaths to be due apparently to contamination of catgut by *Bacillus tetani*.



In another group of cases the pathologic changes were not sufficiently far advanced to disclose the cause of death. In 2 such cases of questionable peritonitis, culture of peritoneal fluid and heart's blood yielded *Streptococcus hemolyticus* in pure culture. In still another group of cases a superimposed pyogenic infection, an important contributory factor, was disclosed only after the routine postmortem bacteriologic examination.

The results show that the spleen serves as well, if not better, than the blood for determining bacteremia, inasmuch as it is more easily cultured and manipulated. Of the 213 cases studied, the blood culture was positive in 80 (38%) of the 206 in which blood cultures were performed, and the spleen culture was positive in 75 (39%) of the 190 cases in which cultures of this organ were made. With reliable technic, postmortem bacteriologic findings are highly valuable. Such studies may strengthen, illuminate, or sharply modify the cause of death, as revealed by clinical and necropsy diagnoses.

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**The Bacteria in Normal and Diseased Lungs of Swine.**

*Robb Spalding Spray, J. Infect. Dis., 31:10, July, 1922.*

This investigation was undertaken to ascertain whether the highly infectious pneumonias so common in swine are associated solely with an infection with *Bacillus suisepcticus*, as seems to be generally accepted. For this purpose, 100 apparently normal lungs of pigs and 314 lungs which showed pneumonic lesions were subjected to bacteriologic study.

Normal lungs showed *B. suisepcticus* in 4% of the 100 specimens. In 2% it was present in pure culture and in large enough numbers to suggest the possibility of impending pneumonia; in the other 2% there were only a few colonies with a mixture of other bacteria. A nonfermenting, typhoid-like bacillus, considered a *Bacillus alkaligenes* type, was found in pure culture in 1 case, and in mixed culture in 2 other cases. An inulin-fermenting streptococcus was isolated from 12% of the cases; in 5 cases there were many colonies present, while in the other 7 cases there were few colonies together with other organisms; no pure cultures were observed. A variety of other organisms, particularly streptococci, were observed in small numbers and always in mixed culture.

Lungs with pneumonic lesions showed *B. suisepcticus* in pure culture in 44% and in mixed culture in 10% of the 314 specimens. The inulin-fermenting streptococcus was present in pure culture in 29% and in mixed culture in 6% of cases. No other organisms appeared in sufficient numbers to indicate any etiologic significance. The 2 strains just mentioned were found in pure culture, or together in approximately equal numbers, in 63% of the 314 specimens. Since the mere presence of *B. suisepcticus* is considered sufficient evidence as to its etiologic significance in swine pneumonias, it would seem that, judged by the same criterion, the streptococcus here described is of almost equal importance.

Because of its ability to ferment inulin, this streptococcus would be classed as a variety within the "mitis" group. (Attention has already been called by Holman to the occurrence of such a variety.) It

is commonly found in clumps of typical Gram positive diplococci. Very pleomorphic strains appear among the first generations on blood-agar, and some of these strains maintain this character indefinitely. Cultures in serum broth and milk display less pleomorphism. Altogether, 128 strains from both normal and pneumonic lungs have been tested. The reaction in each of the culture media mentioned was constant for all strains. Agglutinative typing has so far been carried out only with 1 serum. Out of 63 strains, 19 agglutinated to the full titer of the serum, while the remainder were completely negative. Apparently, the strains will fall in at least 2 agglutinative types. Further work is in progress.

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(1d—64)

**The Bacterial Origin of Dental Caries.**

*James McIntosh, W. Warwick James and P. Lazarus-Barlow, Lancet, 202:1183, London, June 17, 1922.*

The aim in this work was to find a method of isolating the causative organisms of dental caries. The primary factor has been shown to be the acids produced by the fermentation of carbohydrates by bacteria. To determine the degree of acidity necessary to decalcify enamel, non-carious teeth were placed in acid broths of different pH values and left for 34 weeks. A greater degree of acidity than pH 4 was found to be necessary. Then carious material was emulsified in pH 3-5 broth and plates inoculated. The organisms isolated were: Type I, a long, thin bacillus occurring in pairs and chains with a tendency to parallelism, and Type II, short bacilli occurring in chains. Both were nonmotile, Gram positive, facultative anaërobes. These bacilli formed a high degree of acidity by the fermentation of carbohydrates. They resemble in some respects the acidophilus group of Moro, but biologically there are several points of difference. Noncarious teeth were put in glucose broth and inoculated with the bacilli. Lesions similar to natural caries were produced. The name *Bacillus acidophilus* is suggested.

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**Encapsulated Nongas-Forming Bacilli.**

*G. R. Lacy and A. C. Murdoch, J. Infect. Dis., 31:64, July, 1922.*

It is believed that a more detailed knowledge is needed of the group of encapsulated bacilli, particularly since this type is frequently found in infections of the genito-urinary tract. Winslow, Kligler and Rothberg, while giving an admirable classification of the colon-typhoid group, pass by the encapsulated group with a short description of *Bacillus aërogenes* (Escherich) and a few words about the extraordinary variability and the irregular forms of this group. At present, we have 3 well-defined types of encapsulated bacilli: *Bacillus pneumoniae*, *B. acidi lactici* and *B. lactis aërogenes*.

Lacy and Murdoch have succeeded in isolating a previously unrecognized small Gram negative, encapsulated, nongas-forming, aërobic bacillus from 3 patients—a man of 44 years, suffering from chronic cystitis; a woman of 30 years, suffering from pyelitis of the left kidney, and another woman 30 years, suffering from acute and chronic interstitial and parenchymatous nephritis, with many complications. It was not

possible to determine whether the organism was the primary etiologic factor or secondary invader. Each of the 3 stains, when first isolated, was highly pathogenic for guinea-pigs and rabbits, but became less pathogenic after prolonged artificial cultivation.

The bacillus is apparently closely related to that isolated by Meyer and Hinman from a patient suffering from double hydronephrosis. But their organism was hemoglobinophilic, grew in small mucoid colonies, and when smears were made from the growth with a platinum loop the whole colony was frequently removed. None of these statements is true of the bacillus now described, but the cultural reactions are almost identical. There is also a close relationship culturally, and an apparent one immunologically, between the new bacillus and *B. dysenteriae* (Flexner): the antiserum of the latter agglutinates the former.

The authors are of the opinion that the new bacillus should either be placed, along with *B. dysenteriae* (Flexner), in the colon-typhoid bacilli group 2 (according to Winslow, Kligler and Rothberg), or if it does not belong in that group, the other 3 encapsulated bacilli should also be removed from the latter and placed in a separate group together with the new organism.

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#### **Anaërobic Infections.**

*W. Cramer and W. E. Gye, J. State Med., London, 39:254, June, 1922.*

Experimental work has proved that where *Bacillus tetani* and vibron septique, *B. welchii* and *B. oedematiens* are deprived of their toxins, they are unable to infect a susceptible animal. A mixture of a sublethal dose of toxin and an emulsion of any one of these organisms will invariably cause death when injected under the skin. It follows from these accepted facts that it is impossible to explain the occurrence of gas gangrene by the simple infection of a wound with one of these bacilli since that always occurs with the bacteria alone and in the absence of a toxin; an accessory factor must come into operation. The experimental work of the authors proved that the disease begins, not when a wound has become infected with the pathogenic anaërobes, but from the moment when a group of these bacteria have surrounded themselves with a toxin sufficiently concentrated to abolish the local defences of the tissues. This condition is due to a specific local lesion in the tissues which may be brought about by one or more substances, such as ionizable calcium salts, organic and inorganic colloids, or distilled water, capable of rupturing the primary defences before toxin is produced. The organisms multiply rapidly and invade tissues which are often cut off from an active blood supply, or are debilitated by the bacterial poison. Acids are produced, and these promote the pullulation of the microbes and assist the systemic toxic effects by acting on the supra-renal bodies, which are also affected by shocks, fatigue, cold and hemorrhage. This "paralyzed" state of the adrenals favors the invading microbes. A vicious cycle is established which, unless rapidly broken, leads to fulminating disease.

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**The Detection of Anthrax Spores in Shaving Brushes.**

*A. D. Stewart, Indian M. Gaz., Calcutta, 57:204, June, 1922.*

In sending brushes to the laboratory for examination 2 points should be observed: (1) If a case of facial anthrax has occurred and a new brush is suspected, other brushes of the same consignment should be sent, together with information as to where the consignment came from. (2) If brushes of different consignments are sent they should be packed separately. If the patient's brush is the only one available it should be sent separately; in this case the demonstration of anthrax germs in the projecting part of the brush would not incriminate the brush, but if anthrax germs are demonstrated in the buried part of the brush the conclusion is justifiable that these were present when the brush was bought.

In making the cultures enough agar must be poured into the dishes to give a depth of about  $\frac{1}{4}$  in. The growth of spreading surface colonies must be prevented by allowing the agar to dry thoroughly before the covers are replaced. It has been advised to cover the set agar with a thin layer of fresh agar. Stewart has found that this interferes with the extraction of single colonies after cultivation. If the microscopic appearance of the cultures is typical, a guinea-pig is injected with the emulsion of the colony. Should the organism be anthrax, the guinea-pig will die within 2 days and the typical manifestations of anthrax poisoning be manifest. No organism, however typical in culture, should be pronounced anthrax without the pathogenicity test in the guinea-pig. The mouse is more susceptible than the guinea-pig.

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**The Local Inflammatory Reaction Produced by the Tetanus Bacillus.**

*Fred H. Stangl, J. Infect. Dis., 31:22, July, 1922.*

Stangl produced experimental tetanus in guinea-pigs in order to study the reaction of the tissues at the site of inoculation to the tetanus bacilli. He injected 0.25 c.c. of a suspension of the latter (of standard turbidity and of sufficient strength to produce tetanus in guinea-pigs of 250-300 gm.) into the subcutaneous and muscular tissues of the right thigh and also the foot-pad. In the former some of the bacilli reached the thigh muscles so that muscle cell reactions could be observed; in the foot-pad the site of local disease was the same as the site of inoculation frequently encountered in human beings. All animals presented symptoms of tetanus within 12 hours—local tetanus being succeeded by ascending tetanus with opisthotonus, convulsions, and trismus.

Serial microscopic sections of the lesions were made at intervals, from 12 hours after inoculation up to several days after the appearance of generalized tetanus. The earlier sections reveal an intense cellular invasion of the affected area, the polymorphonuclear leukocytes making up about 80-90% of the cells present. In addition, there are a few mononuclear leukocytes and large mononuclear wandering cells. The capillaries are engorged and the endothelial cells enlarged so that they project into the lumen of the vessel. There is also a distinct perivas-

cular infiltration of inflammatory cells. The bacilli occur chiefly in clumps scattered in the spaces between the leukocytes and fixed cells. A few, however, are seen within polymorphonuclear leukocytes, indicating that tetanus bacilli exert a positive chemotaxis and thus confirming Werigo's opinion against Metalnikow. Some of the polymorphonuclear leukocytes are engulfed by large mononuclear wandering cells.

In the older lesions, polymorphonuclear leukocytes become less numerous, while lymphocytes and mononuclear wandering cells make up from one-half to one-third of the cells present. After 5 or 6 days, large fibroblasts are present, and the reparative phase is established. The muscle cells show disappearance of the striations, granular disintegration of nuclei, and waxy degeneration. The formation of giant cells is another characteristic of the later stages.

In one human case, the local reaction (in the sole of the foot) corresponded in all essentials to the reaction of experimental inoculation in guinea-pigs.

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#### **Difficulty of Bacteriologic Diagnosis of Bubonic Plague in a Few Exceptional Cases.**

*Francesco Piccininni, Ann. d'igiene, Rome, 32:277, April, 1922.*

Bacteriologic diagnosis of bubonic plague is usually considered extremely easy, both from the standpoint of the possibility of isolating the microorganisms in appropriate culture media and from the fact that in the guinea-pig we have a true biologic reagent, since this animal is particularly well adapted to such work, one single injection resulting in the appearance of such a characteristic pathologic picture as to be sufficient in itself to establish the diagnosis.

However, the experience gained during the recent plague epidemic at Naples, where isolation of the microorganisms from secretions of 3 patients was obtained only after repeated efforts at culturing, induces the author to believe that in cases of plague of benign course, or on the road to recovery, with extremely mild symptoms, bacteriologic examinations may be beset with difficulties and may lead to erroneous conclusions. Hence, search for the microorganism must be persisted in, and the methods used must be of the most accurate. In all tests (microscopic, cultural, biologic), one must bear in mind that scarcity in numbers or attenuated virulence of the bacteria may yield negative results when isolation of the microorganism from material aspirated from affected lymph glands is attempted, and that only cultural investigation leads to positive findings. Exploratory puncture must be repeatedly affected, extracting the major portion of the exudative material, before a definitely negative report is made and accepted, one single negative result being of absolutely no importance.

These cases have a very great significance also from the standpoint of prophylaxis, since the extremely mild symptoms could easily lead to error of clinical diagnosis. An exact determination of the affection could only be made following microscopic, cultural and biologic tests.



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**Experimental Epidemiology.**

*Simon Flexner, J. Exper. Med., 36:9, July 1, 1922.*

In view of the ravaging epidemics of recent years, it seemed advisable to undertake laboratory studies in epidemiology with the idea of ascertaining their origin, communicability, mode of propagation and methods of control. This subject has been given but scant attention, modern bacteriologic studies being directed mostly to the discovery of incitants of disease. The gains made in the study of etiologic agents has not served to account for all the phenomena of epidemics.

Such phenomena can best be clarified by investigating epidemic outbursts of disease in animals where such epidemics pursue a course similar to that in man. The proper control of microorganism and host can there be obtained for developing the science of epidemiology. This particular investigation of epidemic mouse typhoid was instituted several years ago. Both the microbic agent and the host simulate epidemic conditions in man and therefore are well suited to the study of epidemiologic problems. As with organisms producing human epidemics, the various strains of mouse typhoid bacilli possess identical biologic reactions but differ widely, at times, in their immunologic properties and in pathogenicity. Mice, like humans, manifest varying degrees of susceptibility, some succumbing, others playing the rôle of carriers of infection, and a third group failing to react in any way. In this fashion it is possible to reproduce the evolution of human epidemics. The carrier serves to preserve the virus for further outbreaks, the susceptible animal to maintain the virulence of the microorganism and the succumbing and naturally immune animals act as barriers to further spread of the infection.

It is planned to undertake identical laboratory investigations of respiratory borne diseases as compared with the enteric borne mouse typhoid.

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**An Outbreak of Mouse Typhoid and its Attempted Control by Vaccination.**

*Clara J. Lynch, J. Exper. Med., 36:15, July 1, 1922.*

This paper describes a spontaneous, fluctuating epidemic of mouse typhoid extending over a period of 2½ years at the Rockefeller Institute. Analysis shows that the entire epidemic really consists of 6 individual outbreaks each one of which lasted about 15 days at its maximum intensity. The greater mortality rate occurred among the older mice. As revealed at autopsy through pathologic and bacteriologic studies the majority of deaths were due to the mouse typhoid infection. Of the entire stock of 4282 animals a total of 1463 individuals, or 34%, succumbed during the 2½ year period. Two immunologically distinct strains of this paratyphoid enteritidis organism were recovered. Vaccinations were carried out with suspensions of killed bacilli. Inoculations of only part of the animals rendered the entire stock at the time immune to this particular strain of organism, but did not afford protection against the second type strain of mouse typhoid bacillus. The carrier subject was not investigated thoroughly. Twenty mice which survived the epidemic were studied with this question in mind. In only

1 instance was the offending organism recovered, the cecum of this animal being infected.

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**Experimental Epidemiology. I. An Artificially Induced Epidemic of Mouse Typhoid.**

*Harold L. Amoss, J. Exper. Med., 36: 25, July 1, 1922.*

Author records observations on an epidemic of mouse typhoid conducted under properly controlled experimental conditions. The data so obtained may answer pertinent questions as to origin, mode of spread, and manner of decline of epidemic diseases in general. Mice are the animals of choice for a study of this nature because they can be readily handled in large numbers, and because they are subject to a pathologically and bacteriologically distinct disease, mouse typhoid.

For the animal experimentation, a village was constructed simulating conditions which might obtain with humans. The diet, hygiene, and cages of the animals were scrupulously supervised and the individuals so apportioned as to exclude any extraneous disease. The feeding of the mice and cleansing of the cages were done by one person and always in the same manner. A total of about 500 mice were utilized for the experiments. For inducing the disease pathogenic cultures of *Bacillus typhi murium* were for the most part placed directly into the stomach of the animals through a small silver tube. Two parent strains of the bacillus were employed, both strains being pathogenic for mice when fed directly and also for animals merely exposed to the disease. Each of these strains was shown to consist of individuals of varying virulence. This was demonstrated by comparative studies of the infectivity of the composite cultures as contrasted with single strains obtained originally from the former by the single-cell method of Barber. Two of the strains isolated by the single-cell method failed to incite an epidemic among mice under conditions previously satisfactory for the parent strain.

Following the initial production of the experimental disease, the microorganisms were widely and rapidly disseminated in an entirely unpredictable order. The excrement of diseased animals was the means of conveyance of the infectious material. Progress of the epidemic depended on dosage, fluctuations in pathogenic activity of the bacillus and resistance of the host. Animals which succumbed were always examined for the characteristic lesions and confirmatory bacteriologic studies performed. The organisms so recovered were then subjected to special cultural and serologic methods for purposes of accurate identification.

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**Experimental Epidemiology. II. Effect of the Addition of Healthy Mice to a Population Suffering from Mouse Typhoid.**

*Harold L. Amoss, J. Exper. Med., 36: 45, July 1, 1922.*

Observations are recorded on the effect of bringing normal mice into a community in which mouse typhoid is prevailing. A study of 12 such consecutive replacements forms the basis of the report. A patchy, sporadic outbreak of mouse typhoid can be induced by bringing a small number of mice previously fed with culture of *Bacillus typhi*

murium into contact with healthy mice—immediacy of contact is not essential. Despite the wide distribution of the infectious agent as a result of the sporadic outbreak the death rate remains low and the particular outbreak rapidly wanes. The sporadic outbreak, when practically at an end, can be made to assume epidemic proportions by the further addition of healthy animals. A consistent train of events ensues in an orderly manner for 2 reasons, augmented virulence of the microorganism as a result of repeated passage through animals and actual increase in numbers of microorganisms which are capable of further infecting animals. The addition of new healthy mice serves to maintain the death rate.

The second epidemic spread, following the addition of the new mice, progresses in a definite predictable manner. The recently added mice begin to succumb within 5 days, the death rate and number of attacked cages rising daily. During the period when the new mice are being infected, the original, previously infected mice remain free from disease. The old mice, however, are again drawn into the epidemic within 10 days after the addition of the new mice, or, 5 days after the latter commence to show evidences of infection. The fatalities then continue up to the twentieth day following the introduction of the fresh mice. Upon the establishment of a state of equilibrium between unaffected animals and the bacillary incitant, the epidemic subsides before all the exposed mice are afflicted. These epidemic waves can be reproduced repeatedly and in classic manner.

The experiments prove that mice which have survived 1 epidemic spread are not immune to eventual attack in any of the succeeding epidemic waves. No definite protection is afforded any of the mice by long survival in epidemics. Those survivors in whom little or no agglutinins could be demonstrated in the blood were more liable to eventual death than those in whose blood specific agglutinins could be found, the relative death rates being in proportion of 4 to 1. Active immunization of animals can be accomplished by intrastomachic injection of living or killed mouse typhoid bacilli, under proper conditions.

Check of the epidemic spread is brought about in a twofold manner: (1) by a tendency of the infectious agent to return to an average of infectivity; and (2) by the greater resistance of certain mice which serve to delimit growth and multiplication of the bacilli.

The rôle of carriers has not been definitely determined. The presence of carriers must be detected by both cultural and immunologic tests. With bacteriologic studies alone one may be led astray by the recovery of foreign microorganisms belonging to the broad, loosely termed group of mouse typhoid bacilli.

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#### **Experiments on Normal and Immune Mice with a Bacillus of Mouse Typhoid.**

*Leslie T. Webster, J. Exper. Med., 36:97, July 1, 1922.*

Normal mice were regularly infected when injected intrapleurally or intraperitoneally with the bacillus of mouse typhoid used in these experiments. Following an initial lag of 4 to 6 hours after inoculation

of the animals, bacterial multiplication proceeded at a rapid rate until death of the animal ensued, usually within 8 days. Animals succumbing to the acute illness showed few pathologic changes. Mice could not be so uniformly infected with organisms introduced per os. Animals successfully inoculated in this fashion first manifested evidence of disease after an incubation period of about 5 days. The clinical course was more prolonged, the lesions at necropsy being consequently more extensive, definite, and of a chronic nature. The virulence of the microorganisms was depressed or completely suppressed when inoculated into animals previously vaccinated with killed cultures by the intraperitoneal, intrapleural, or subcutaneous route. The protection gained by vaccination, as shown by immunologic reactions, was entirely of a general nature; a local immunity could not be demonstrated.

It was possible to immunize animals by the gastro-intestinal route. Mice fed with killed or living cultures of bacillus of mouse typhoid were protected against lethal doses of living bacilli introduced per os or intraperitoneally. The immunity in this manner was similarly found to be of a general nature.

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**Identification of a Paratyphoid-Enteritidis Strain Associated with Epizootics of Mouse Typhoid.**

*Leslie T. Webster, J. Exper. Med., 36: 97, July 1, 1922.*

The strain of mouse typhoid bacillus under investigation presents morphologic and cultural characteristics which place it in the paratyphoid-enteritis group. It is Gram negative, motile, nonsporulating bacillus. Agar colonies are thin, bluish, and somewhat translucent, with irregular edges. Dextrose, levulose, maltose, mannitol, xylose, arabinose, rhamnose, and inositol are fermented. Gas is formed, milk is not coagulated, indol is not produced, lead acetate medium is blackened. Accurate identification is obtained by serologic means. By such tests this particular bacillus was identified with *Bacillus pestis caviae* Smith and found closely related to the type "mutton" aertrycke strain of Schütze. The *Bacillus pestis caviae* is capable of producing similar epizootics in guinea-pigs.

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**Immunologic Distinctions of Two Strains of the Mouse Typhoid Group Isolated During Two Spontaneous Outbreaks Among the Same Stock.**

*Harold L. Amoss and Peter P. Haselbauer, J. Exper. Med., 36: 107, July 1, 1922.*

Within a period of 2½ years 2 distinct outbreaks of mouse typhoid were encountered among the 2500 to 400 mice maintained at the cancer breeding station of the Rockefeller Institute. One of the several strains of organisms of the paratyphoid-enteritis group isolated in the first sporadic outbreak was employed for production of an artificial epidemic for experimental purposes. This strain, referred to as mouse typhoid I, was first passed through a series of mice to enhance its virulence. The organism, mouse typhoid II, recovered from the spleen of the fourth member of this series was found to be identical culturally with mouse

typhoid I but not serologically. Specific antiserum prepared against mouse typhoid I did not agglutinate mouse typhoid II. This replacement of mouse typhoid I by mouse typhoid II in the inoculated series may be due to the presence of the latter microorganism in 11 of the animals previous to the experiment.

Comparative agglutination and absorption tests were done with a variety of microorganisms in an attempt to further identify and differentiate strains of mouse typhoid I from mouse typhoid II. Mouse typhoid I antiserum completely agglutinated the following animal typhoid strains; mouse 2, rat, guinea-pig, and dog 1. Mouse typhoid II antiserum failed to agglutinate these organisms but did contain agglutinins for the calf typhoid strain. Mouse typhoid I, in addition, was found to be related but not identical with 2 enteritis cultures, while mouse typhoid II was related to but not identical with human paratyphoid B strains.

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#### **Development of Paratyphoid-Enteritidis Group in Various Foodstuffs.**

*Stewart A. Koser, J. Infect. Dis., 31:79, July, 1922.*

The object of this investigation is to gain some idea of the ability of several type strains of the paratyphoid-enteritidis group to develop in miscellaneous foodstuffs (vegetables, fruits, meats, evaporated milk). As a rule, canned foods were used, as this procedure closely simulated conditions in the household where, after the partial consumption of cooked food, the remainder is set aside for further use. As the behavior of the different organisms was quite similar, detailed results are presented only with respect to one type, namely, *Bacillus enteritidis* ("Brighton") strain.

In tomatoes, spinach, string beans, corn, peas, and in evaporated milk, these organisms were found able to multiply in various degrees, but not in highly acid sauerkraut. The growth in tomatoes was surprising in view of the acidity of the product. In tomatoes, spinach, corn and string beans, there occurred, at 37°C., a rapid growth during the first 24 or 48 hours, followed by an abrupt decline in numbers. This rapid decrease is correlated with a high pH. In peas and evaporated milk, in which the decline was not abrupt but gradual, the change in pH was toward an alkaline reaction. In the fruit juices, a rapid destruction of the organisms occurred. In the meat products (corned beef, Hamburg steak, red salmon), the organisms exhibited marked ability to spread from one original point of inoculation throughout the foodstuff, but only under optimum temperature conditions. The extent of the contamination is determined by the moisture and texture of the various foodstuffs.

In accordance with observations during previous outbreaks of "food poisoning" caused by this group of organisms, the appearance, smell and taste of the various foodstuffs was normal in practically all instances. The only exceptions were a thin white surface pellicle in the case of peas, and some evidence of gas formation in several of the food products, especially peas and corn.



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### **The Human Aertryckoses.**

*A. Besson and V. de Lavergne, Ann. de l'Inst. Pasteur, Paris, 36: 502, June, 1922.*

The authors have made comparative studies with paratyphoid B bacilli. There has been considerable confusion concerning the possible identity of *Bacillus aertrycke* and Schottmüller's bacillus. Bacteriologically, the two species are proved by the authors to be quite distinct. An antityphoid B serum (blood infection) does not agglutinate paratyphoid B bacilli of the stools. Crossed immunity, as shown in 5 guinea-pigs tested for each bacillus, also proves that the two bacilli are different. *Aertrycke's* bacillus is more resistant than Schottmüller's to malachite green. The paratyphoid B of blood infection is identical with Schottmüller's paratyphoid B. The paratyphoid B of stool infection has the same characteristics as *Aertrycke's* paratyphoid B. The latter may therefore be determined bacteriologically.

Clinical studies were made in 4 cases of diarrhea, 1 of which was fatal. *Bacillus aertrycke* was found in the stools of all. In man it seems that aertryckosis may cause not only an acute gastro-enteritis due to food intoxications, but a simple diarrhea or the symptoms of cholera nostras. Infection may occur in various ways, such as through food poisoning, meat, water, or fruit. Dust, flies and dirty hands transmit the infection. The bacilli may exist in the intestine of carriers. Immunity to Schottmüller's bacillus does not protect against *B. aertrycke*. For diagnosis of aertryckosis, blood cultures are valueless. Serum diagnosis may be utilized if the condition is well defined and of considerable duration. Agglutination will usually be positive for both bacilli, and saturation tests will probably be required. Emulsions must not be thick and incubation must not exceed 2 or 3 hours. The English technic is applicable. Cultures should be made of bacilli from the stools. Indol production is important, indicating the absence of the Schottmüller or *Aertrycke* type. If a little gas is produced in a lactose culture, a saccharose culture will determine Castellani's diagnosis. If neither sucrose nor mannite are attacked, Morgan's result is shown. If a paratyphoid B bacillus is present, agglutination tests with anti-*aertrycke* and anti-Schottmüller serums are made. If the first is positive and the second negative, the diagnosis is clear. If agglutination is produced in both cases by nearly the same quantity of serum, saturation is done with incubation not over 2 hours. The serums are then tested against a known Schottmüller bacillus, known *B. aertrycke* and the unknown bacillus. An agglutinating serum for the unknown bacillus may be prepared and the tests repeated. If the cultural characters of the unknown are those of paratyphoid B. but if neither antiaertrycke nor anti-Schottmüller serum agglutinates, there are 3 possibilities: the unknown is a Gaertner's bacillus, a paratyphoid C bacillus or *B. aertrycke* or Schottmüller's bacillus which will become agglutinable with age. Aertryckosis thus constitutes a clinical entity.

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**Infectious Motor Paralysis in Young Rabbits.**

*J. Homer Wright and Eugene N. Craighead, J. Exper. Med., 36: 135, July 1, 1922.*

This disease was encountered in inoculated and control rabbits in the course of studies on the mode of transmission of anterior poliomyelitis. Afflicted rabbits become lethargic, later develop tremors which are followed by irregular paralysis of varying degree and localization. The mortality is high. Cultures of blood and various organs are uniformly negative. Blood smears examined during height of the disease are likewise bacteria free. Upon examination of the central nervous system, postmortem, no characteristic gross lesions are found. The essential inflammatory process found upon microscopic examination of the brain and cord is a focal infiltration with small round cells. Polynuclear leukocytes take no part in this process. With disappearance of the nervous-tissue elements in this area vascularization takes place. The vessels of the pia mater occasionally show perivascular mononuclear cell infiltration. The diffuse pathologic picture accounts for the clinical manifestations of the disease.

By appropriate staining methods peculiar bodies, believed to be microorganisms, can be demonstrated in most of the lesions. These are elongated, bacilloid, irregularly staining bodies having round or conical ends. There is slight tendency to pleomorphism. Their dimensions rarely exceed  $4 \times 1.5$  microns. They stain by Gram's method and with methylene-blue. No nuclear structures are present. They are acid fast to a certain extent. The optimal staining method consists in first exposing the section to dilute carbol fuchsin (diluted 1-4), then mordanting and decolorizing with undiluted formaldehyd, and finally counter-staining with methylene-blue. With this method the microorganisms appear red as against deep-blue staining nuclei.

The organisms are found in varying numbers in the lesions. Occasionally they develop marked invasive properties, the destroyed nerve cell being at times transformed into a shell containing masses of these bodies. Identical focal lesions containing these microorganisms are found widely distributed throughout the organs such as kidney, spleen, liver and myocardium. The same organism, morphologically, can be discovered in the urine during life. Contact spread of the disease is thus readily explained. The exact nature of this organism has not been determined. They probably represent an intermediate stage in the development of some protozoan parasite.

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**Experimental Production of Bovine Mastitis with Streptococci and Other Bacteria.**

*C. M. Carpenter, J. Infect. Dis., 31: 1, July, 1922.*

These experiments were undertaken to ascertain the ability of certain bacteria to produce mastitis in cattle and also to inquire into questions of immunity. With the exception of *Bacterium pyocyaneum* and *Pasteurella bovis septica*, the organisms were isolated from cases of mastitis and from diseased genital organs of cattle. Thirteen animals, ranging from  $2\frac{1}{2}$  to 11 years, were used for this work, after the milk

from the 4 quarters of each udder had been subjected to a bacteriologic examination. The injections were made by means of a small teat cannula fitted to a 10 c.c. record syringe, immediately after the animal had been milked (about 4 p. m.).

Milk containing hemolytic and nonhemolytic streptococci from infected udders produced a more severe mastitis than 24 hour broth cultures of the same organisms when equal amounts were injected into the teat canals of healthy cows. Whether this is due to the organisms losing their virulence immediately on artificial cultivation, or to the metabolic products formed in the milk by the streptococci, cannot yet be determined. With hemolytic streptococci, the reaction was less severe, and the difference between milk and culture less marked than with nonhemolytic streptococci.

*Streptococcus viridans*, *Bacterium abortum*, and *Bacterium pyocyaneum* usually produced only a slight swelling of the quarter infected, with the formation of a few flocculi of pus in the milk, and the mastitis cleared up in 48-72 hours after injection. *Bacillus coli* produced an acute mastitis, which cleared up 8 days after injection. This coincides with Jansen's work on organisms from the colon-aërogenes group. *Staphylococcus aureus* and *Pasteurella bovisepctica* produced a severe mastitis with general symptoms and an acute local condition, which destroyed the functional activity of the gland. The degree of mastitis produced was influenced by the age of the animal and the amount of milk given at the time of injection. Heifers were much more susceptible and suffered more severely.

Subcutaneous injection of suspensions of the dead organism that had produced the mastitis did not effect a cure. In a number of cases, an attempt to immunize the animal was made by the subcutaneous injection of suspensions of the dead organisms during 15 days in gradually increased amounts. A month later, a live culture of the same organism was injected. The check animals showed no more inflammation of the udder than those receiving the dead suspensions. The subcutaneous injection of milk from the infected quarters seemed of no value and in some cases produced large abscesses on the animal.

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#### The Streptococci of the Bovine Udder. IV. Studies of the Streptococci.

*S. Henry Ayers and Courtland S. Mudge, J. Infect. Dis., 31:40, July, 1922.*

The authors studied 100 cultures of streptococci obtained from 55 samples of milk (from 54 cows) for the purpose of determining the various kinds. Of the 11 groups into which the 100 cultures are divided, 4 (comprising 79 cultures), designated A, B, C, D, are described as representing together the *Streptococcus mastitidis* (Guillebeau), which thus appears as the "typical udder type". There are 2 varieties of this organism, the one hemolytic (groups A and B), and the other nonhemolytic (groups C and D). The difference between A and B and between C and D, respectively is that the one group ferments salicin and the other does not. The following characteristics are common to all 4 groups and may be described as the general charac-

teristics of *Streptococcus mastitidis*. It ferments dextrose, lactose and cane, and does not ferment mannite, raffinose and inulin. It produces  $\text{CO}_2$  and  $\text{NH}_3$  from peptone, but no  $\text{CO}_2$  from dextrose. It hydrolyzes sodium hippurate into benzoic acid and glycocoll.

According to Holman's classification, Group B would be called *Streptococcus pyogenes*, and so would 23 out of 33 cultures derived from human sources, mostly from pathologic conditions, which were studied for purposes of comparison. Indeed, on the basis of hemolysis and positive or negative fermentation, the 2 groups (in other words: *S. mastitidis* and *S. pyogenes*) would be identical with each other. But they are quite different in other respects. Above all, the pH reached in the fermentation of test substances is distinctly different (udder type 4.5 and human type 5.5 in a dextrose yeast peptone broth). Another difference appears in the negative hydrolysis of sodium hippurate by the human type.

Of the remaining 7 types, 4 (comprising 12 cultures) are of special interest in that they represent what seems to be a new species, described as *Streptococcus acidominimus* because of the small amount of acid produced in test substances. It is shown that the same species of streptococcus which are present in mastitis are frequently found in the udders of normal cows. The fact that milk containing these organisms has been consumed regularly with no ill effects indicates that they are not pathogenic for man. This is confirmed by the animal experiments of Nocard and Mollereau and of Jones.

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(1d—82)

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**On the Biologic Properties of Pathogenic Molds.**

*Sigmund S. Greenbaum, J. Infect. Dis., 31:26, July, 1922.*

After 18 months' study of the growth of ringworms, obtained from Sabouraud, on various culture mediums of American made ingredients, the author has, with other investigators, come to the conclusion that, for the present, recognition of any of these organisms depends on their characteristics developed on mediums made with the French ingredients (difficult to obtain in America) and the methods used by Sabouraud. Under these circumstances, it appears that a definite conception of the ringworm flora of America can be arrived at only by investigation of the biologic properties of these pathogenic molds, which have so far been almost totally ignored, although their proteolytic ferments have been studied by several investigators whose results are summarized. Greenbaum's own study covered 5 points:

(1) Proteolytic ferments. The organisms studied are divided into 4 groups according to their comparative proteolytic properties (in 10 c.c. of 10% gelatin), i. e. the degree of liquefaction at the end of 24 hours. Complete liquefaction: *Trichophyton niveum* radians, *T. vinosum*, *Microsporon pubescens*, *Achorion quinckeanum*. Moderate liquefaction: *T. violaceum*, *T. fumatum*, *T. lacticolor*, *Sporotrichum beuermannii*, *S. schenki*. Slight liquefaction: *Trichophyton crateriforme*, *T. acuminatum*, *T. sulphureum*, *T. exsiccatum*, *T. cerebriforme*, *T. plicatile*, *T. gypseum asteroides*, *T. granulosum*, *Microsporon lanosum*. No liquefaction after 24 hours, but at a later stage: *Thichophyton rosaceum*, *Microsporon audouini*, *M. fulvum*, *Sporotrichum gougeroti*,

*Actinomyces bovis*, *Achorion schönleinii*, *A. gallinae*. Apparently, gelatinase is a common property of the higher vegetable parasites and varies with the organism, but not in proportion to the rapidity of its growth—*Trichophyton gypseum asteroides*, e. g., is a "quick grower". The solubility of this ferment also varies with the organism and is altogether absent in some cases, as is shown by the action of filtered liquefied gelatin on fresh gelatin.

(2) Amylolytic ferments. The pathogenic molds possess no amylolytic properties.

(3) Sugar fermentation and litmus reaction. The trichophytons, microsporons and achorions enumerated above do not ferment saccharose, dextrin, glucose, levulose, maltose or lactose, and they produce no acids or bases.

(4) Indol production. Böhme's technic produced negative results.

(5) Toxin production. Guinea-pigs injected intraperitoneally with bouillon cultures of (4 c.c.) *Trichophyton acuminatum*, *T. gypseum asteroides* and *Achorion schönleinii*, died, whereas *Microsporon audouini*, *Sporotrichum beuermanni*, and the medium control gave negative results. This latter fact would seem to disprove Sabouraud's opinion that the resultant effects of inoculation are due to the toxic action of the peptones. The appearance after death (marked suprarenal vascular injection) was similar to that produced by the intraperitoneal injection of diphtheria toxin.

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**The Infection of Lice (*Pediculus Humanus*) with *Rickettsia Prowazeki* by the Injection per Rectum of the Blood-Platelets of Typhus-Infected Guinea-Pigs and the Reinfection of Other Guinea-Pigs from These Lice.**

*A. Bacot and J. Segal, Brit. J. Exper. Path., London, 3: 125 June, 1922.*

Female specimens of *Pediculus humanus* were given an infecting meal of platelet material obtained by fractional centrifugation of the blood of typhus-infected guinea-pigs. These lice were thereafter given rectal injections of defibrinated normal human blood. The lice were incubated at 32° C. and fed twice daily for the major portion of the period following heavy bacterial contamination of the alimentary tract. The development of *Rickettsia prowazeki* was ascertained by dissecting out the guts of specimens which died and making smears of the macerated intestines. Guinea-pigs infected with an emulsion of the organs of these lice gave typhus reactions. Lice infected by the rectal injection of an emulsion of the gut of infected lice through 4 generations of lice showed *Rickettsia prowazeki*, while guinea-pigs infected with an emulsion of guts of lice of the fourth passage from insect to insect showed typhus reactions.

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**Pure Cultures of *Spirochaeta Pallida* in Solid and Liquid Culture Media and the Transmission of These Cultures to Animals.**

*A. von Wassermann and M. Fisher, Klin. Wchnschr., Berlin, 1: 1101, May 27, 1922.*

After years of work the authors have succeeded in cultivating  
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7 pure culture strains of *Spirochaeta pallida* on fluid and semifluid nutritive media. With these cultures they have been able to produce typical syphilis in rabbits. This strain can now be transmitted from animal to animal. Ficker was the first to succeed in taking a pure culture of a rabbit strain that had been produced experimentally, and obtaining it again in pure culture from the infected rabbit. Attempts to obtain toxins or hemolysins with a general action from the pure culture have not so far been successful. The recovery of the pure cultures led the authors to make experiments in giving killed spirochetes together with spirillocide salvarsan, in an attempt to produce greater amounts of antibody and thus affect the further course of the infection. It will not be possible to pass judgement on the success of these experiments for some years. They prophesy that in the future the present method of treatment will appear mechanical, and that much greater attention will be paid to the allergy of the tissues and the presence of agglutinating and spirillocide substances in the serum, which seem to play an especially important part in certain diseases, for instance in aortic changes.

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**The Structure and Systematic Position of *Strongylus Polygyrus*.**

*C. L. Boulenger, Parasitology, London, 14:206, June, 1922.*

The author obtained a number of strongylids from the intestine of *Microtus (Arvicola) agrestis* L. from the neighborhood of Birmingham. He believes the specimens obtained from the Birmingham voles agree with those described by Dujardin and von Linstow in so far as the shape of the tail and the position of the anus are concerned. The vulva was found to be situated 0.24-0.35 mm. from the posterior extremity. Boulenger gives a revised diagnosis of the genus *Heligmosomoides*, together with a new specific diagnosis of *H. polygyrus* based on his experimental material. The revised diagnosis is: *Heligmosomoides* Hall, 1916, belongs to genus *Heligmosominae*. The body is commonly coiled in a spiral, with transverse and longitudinal striations. The male has long, filiform spicules. The bursa are without separate dorsal lobe or middorsal incision. The dorsal ray is very short with 4 small branches. The externodorsal rays are long and slender, with separate origins. The lateral rays rise from a common trunk and are divergent. Ventroventral and lateroventral rays diverge from a common origin. The Prebursal papillas are long. The female has a truncated posterior extremity bearing a slender caudal spike, the vulva being situated posteriorly. Type species: *H. polygyrus* (Dujardin, 1845).

The article is illustrated by 4 text-figures of *Heligmosomoides polygyrus*.

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**A Parasitic Copepod Belonging to the Genus *Medesicaste* (Krøyer), and Its Relation to the Tumors It Produces on the Fish, *Trigla Gurnardus*.**

*W. Harold Leigh-Sharpe, Parasitology, London, 14:214, June, 1922.*

The author made the following observations on 8 specimens of  
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Medesicaste taken from various *Trigla gurnardus*. They were, without exception, upon the gills, upon which they cause characteristic tumors. The head of the animal is 1.4 mm. long, bulbous, trilobate, rounded in front, with each side expanded into a hemispheric lobe. The enlarged posterior portion of the neck, is 1.8 mm. long. Both head and neck as far as the mouth are embedded in the tumor which is formed upon the gill filaments of the host. The trunk is square in outline and divided by a deep transverse constriction into 2 almost equal parts, the anterior constituting the thorax bearing appendages, carrying 2 pairs of obtuse processes ventrally and a small pair dorsally, the posterior and larger, the genital segment, the anterolateral corners of which extend outward into angular projections. The abdomen is very small, biarticulated, the posterior segment being the larger, and enclosed between the posterolateral lobes. There are no abdominal appendages. The appendages, all paired, none of them setigerous, are, in order, as follows: the antennae, the mandibles, and 2 pairs of maxillipedes. The tumor among the gill filaments of *Trigla gurnardus* bears a female medesicaste with the head and neck buried in its apex, and a male medesicaste completely embedded in its base. The 2 sexes of the parasite are connected by a conjugation tube, external to the tumor, down which tube the spermatophores presumably pass.

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(1d—87)

(1d—87)

**The Development of *Heligmosomum Muris* Yokogawa, a Nematode from the Intestine of the Wild Rat.**

*Sadamu Yokogawa, Parasitology, London, 14:127, June, 1922.*

The author remarks that the postembryonic development of nematodes is very insufficiently known. *Heligmosomum muris*, which Yokogawa described from the rat in 1920, proved to be very good material for the study of development during the parasitic stages. This form is small and develops in ordinary culture rats as well as in wild rats. Moreover, infection can easily be obtained and its development in the rat requires only a few days. This made it possible to obtain an abundance of material of the stages of development and to secure at any time material of any particular stage on which further observations were needed. Yokogawa's observations were made from living specimens. To find the larvae in the lungs of the experimental rats it is necessary to divide the tissues into very small pieces in normal salt solution, and then to crush carefully in a mortar and filter through a fine wire screen. The filtrate is then centrifuged and the larvae if present can be recovered. After the larvae have made their way to the intestine it is easy to pick them from the surface of the mucous membrane.

Yokogawa divides the postembryonal development of *H. muris* into 5 stages, 2 free and 3 parasitic, with 3 moults. There is only one moult during free life, the second and third stages being separated by change of habitat brought about by entrance into the host. Sexual maturity is attained soon after the completion of the third moult. Infection of the rat can be accomplished both by way of the mouth or through the skin, the latter being the more effective. The larvae reach the lungs 14-20 hours after penetrating the skin. They remain in the lungs until 35-65 hours after infection; the majority of them reach the intestine 50-65 hours after infection, although they are sometimes found there

as early as 45 hours. In the lungs the larvas increase rapidly in size and moult just before they migrate to the intestine. Early in the development in the lungs the sexes can be distinguished by: the migration toward the posterior end of the genital primordium of the female, structural differences in the caudal region, and differences in shape of the genital primordium. After reaching the intestine the larvas grow rapidly and enter into the third moult 96-108 hours after infection. In the fourth larval stage between the second and third moults growth and differentiation are most marked. It is during this stage that the differentiation of the organs of the reproductive system occurs.

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(1d—88)

(1d—88)

**A Synopsis of the Family Linguatulidae.**

*Louis Westenra Sambon, J. Trop. Med. & Hyg., London, 25: 188, June 15, 1922.*

The taxonomic rank of Linguatulidae has been a puzzle to zoölogists and continues in controversy. The author has studied a considerable number of linguatulids in their various developmental stages, from egg to adult, and is of the opinion that these wormlike organisms should be regarded as greatly modified endoparasitic descendants of Acarina. To the structural features adducted by Leuckart to prove their acarine nature, Sambon adds some new and important ones, such as the anterior position of the female genital opening, a sacciform uterus and 6-legged larvas which characterize the genera Raillietiella and Reighardia. A classification of Linguatulidae is submitted, with brief description of all known species and lists of separate indexes of the regional distribution, known hosts and various synonymys of each species.

The family Linguatulidae comprises 2 subfamilies, Raillietiellinae and Porocephalinae. The subfamily Raillietiellinae comprises 2 genera, Raillietiella (6 species) and Reighardia. The type species of Reighardia Ward, 1899, is Reighardia sterna (Diesing, 1864) Ward, 1899. The subfamily Porocephalinae is divided into 3 sections, Sebekini, Porocephalini, and Linguatulini. Sebekini comprises 3 genera, Sebekia (6 species), Alofia (3 species) and Leiperia. Leiperia cincinnalis (Sambon, 1910) Sambon is the only species in genus Leiperia Sambon, 1922 n. sp. Porocephalini comprise 4 genera, Porocephalus (4 species), Kiricephalus (3 species), Armillifer (3 species) and Waddycephalus. Waddycephalus (Baird, 1922). Sambon, 1922, is the only species in Genus Waddycephalus Sambon, 1922. Linguatulini comprise 2 genera, Linguatula (2 species) and Subtriquetra (2 species).

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(1d—89)

(1d—89)

**Some Notes on Indian Calliphorinae. Part VII. Additional Cases of Myiasis Caused by the Larvas of Chrysomya Bezziana Vill., Together with Some Notes on the Diptera Which Cause Myiasis in Man and Animals.**

*W. S. Patton, Indian J. M. Res., Calcutta, 9: 654, April, 1922.*

As examples of human myiasis, a number of larvas were found in a sloughing ulcer on the external orbit of a female patient and a number of young third stage larvas were collected from the internal ear (Sec. 1—Page 305)

of a youth of 18. In the latter case an ant had crawled into the ear, which had been syringed out by a native doctor, yielding a blood-stained fluid. A number of third stage living larvas were taken from the nose of a female patient aged 30 who eleven days previously had had a discharge from the nose, Flies had sat on and around the nose. Many maggots were removed from the nose, and several crawled out of their own accord. A number of living larvas were taken from an abscess on the scalp of a girl of 10. Several living larvas were collected from a septic wound on the face, and some were taken from a sloughing ulcer on the scrotum, some from an ulcer on the right temple of a child. A number of hatched flies and puparia, as well as larvas, were also found in a sloughing ulcer on the penis of a boy following circumcision. A number of puparia of *C. bezziana* were removed from the nose of a male patient aged 45. Dead larvas were collected from the vagina of a patient complaining of difficulty in micturition; others were taken from a sloughing ulcer on the right foot of a patient of 30, and a number from a gangrenous sore on the knee. In animal myiasis, larvas were collected from a sore on the back of a bull buffalo, from the cancerous ulcer on the vulva of a cow, from the base of a broken horn of a cow, from a wound following removal of a fibrous tumor on the neck of a bullock, from the vagina of a cow where they had burrowed deep into the vaginal wall, and from the eyeball of a cow, a papilloma having ulcerated and attracted *C. bezziana*, the larvas having burrowed into the eyeball and completely destroyed it. Larvas were also collected from the penis sheath of a horse, and from a girth wound on an aged donkey. The efficient protection of all wounds and ulcers in any part of the human body is of the first importance, and when invasion has occurred, all larvas should be destroyed and not allowed to crawl away and pupate.

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(1d—90)

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**On the Larval Development of *Dacnusa Areolaris* Nees (Braconidae), a Parasite of *Phytomyzinae* (Diptera), with a Note on Certain Chalcid Parasites of *Phytomyzids*.**

*Maud D. Haviland, Parasitology, London, 14:167, June, 1922.*

The author studied the leaf-mining fly *Phytomyza angelicae* Zett which had infested the wild angelica, (*Angelica campestris*.) About 60% of the larvas collected were found to contain an endoparasitic braconid, *Dacnusa areolaris* Nees. No other internal parasite was present which simplified working out the development of this form. The author found that the larva of *Phytomyza angelicae* mines into the leaves of *Angelica campestris*, forming irregular discolored blisters on their surface. When fully fed, the larva leaves the leaf by a slit on the under surface of the blister, and falls to the ground where it pupates. The imagos usually emerge 19-20 days later, but the pupal period may be prolonged up to 25 days. In captivity, pairing and oviposition took place a few hours after emergence, and the flies lived only 1 or 2 days.

The phytomyzid is liable to attack by *D. areolaris* only in the earliest larval stages when less than 0.5 mm. in length, and older larvas seem to be immune. The egg is laid and development takes place within the body of the host. A membrane of trophic cells is formed, within

which the embryonic and first larval stages are passed. The further growth and development of the parasite are delayed until after metamorphosis of the host, probably to insure sufficient food in the later stages. The length of the larval and pupal life of the parasite is intimately correlated with the puparial period of the host. The author suggests that this may be an adaptation to ensure that an adequate supply of host larvae shall be hatched by the time the parasites are ready to oviposit.

Collections of *Phytomyza angelicae* showed that while there was still considerable infestation by *D. areolaris*, 80% of the fly larvae had been either parasitized or epiparasitized by certain ectoparasitic chalcids. The author had them examined and they were then referred to the genera *Chrysocharis*, *Eulophus* or *Hemitarsus* of the subfamily *Eulophinae*. The larvae feed externally upon the host, and are of the usual type of chalcid larva. As development proceeds, the larvae increase in size, but do not change materially in form. The host dies soon after the parasite has begun to feed, and in 5 or 6 days only the empty skin is left, together with the calcospherites, or crystalloid concretions of certain cells of the fat body. These chalcids weave no cocoon, but undergo metamorphosis within the blister on the leaf. The pupal period is about 4 weeks.

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(1d—91)

(1d—91)

**A Contribution to the Knowledge of the Hippoboscidae (Diptera Pupipara).**

*G. F. Ferris and F. R. Cole, Parasitology, London, 14: 178, June, 1922.*

In the course of its development the study of practically all the ectoparasitic groups of insects has passed through certain fairly well-defined stages. Beginning with pinned material, even in those groups the members of which are the most fragile, it has progressed through various types of inadequate preparations resulting finally in the development of a specialized technic for the production of microscopic preparations, which requires a considerable degree of skill. In the preparation of slide mounts of hippoboscids the authors have utilized the following procedure. In the case of winged specimens the wings are detached and mounted directly. The body is boiled in a 10% solution of caustic potash until the contents are entirely liquidified. It is then transferred to water, judiciously placed slits are made in it and the contents carefully pressed out. In the case of these insects this is difficult because of the highly developed network of tracheas within the body. The specimen is next transferred to 95% alcohol for a few minutes, then to carbolxylene and finally mounted on balsam. In most cases it is desirable to support the cover-glass on bits of broken glass in order to avoid distortion of the specimen. The article is accompanied by 20 figures which for the most part, are corrected camera lucida sketches of specimens examined by Cullen's method.

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(1d—92)

(1d—92)

**The Biology of a Keratopogoniate Blood-Sucking Insect. (Holoconops Mediterraneus, J. J. Kiefer, 1921).**

*Etienne Sergent, Arch. d. Inst. Pasteur de l'Afrique du Nord, Algiers, 2:119, March, 1922.*

This insect occurs abundantly throughout the summer in the cliff region of the Algerian coast, extending from Ain-Taya to Jean-Bart. It can scarcely be seen during flight. At rest, the thorax and wings form a triangular black point and tiny grayish rectangle. The insect attacks man during the warmer part of the day, between 9 and 5 o'clock, biting especially in shady places sheltered from the wind. It rarely enters dwellings. It is especially active on cloudy and stormy days. The regions which it attacks are, in the order of frequency, the postero-external region of the forearm, the hands, nucha, face and uncovered parts of the legs. When perched upon the skin, it does not bite immediately, but runs about for short distances; 6 times to 10 it is not felt unless it strikes a hair. When at rest, its long abdominal axis is oblique to the skin. While biting, the head is lowered and the abdomen becomes parallel to the skin. The anal orifice and sting open and close while the insect feeds. Sucking lasts 2 to 3 minutes, or more. A slight burning sensation is produced, provoking scratching. In about a third of the cases it is absent, and disappears in all cases very soon after the insect leaves the skin. The insect gorges itself in a single meal, the abdomen becoming filled with blood.

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## **1e. IMMUNOLOGY, SEROLOGY AND HEMATOLOGY**

(1e—60)

(1e—60)

**Experimental Investigations on Phagocytosis. Modifications of Phagocytic Property Through the Action of Alkalis on Bacteria, Serum and Leukocytes.**

*G. Di Macco, Haematologica, Naples, 3:273, May, 1922.*

Phagocytosis is unfavorably influenced by alkaline substances, through some action of the latter on leukocytes and their properties, on the activating substances contained in blood serum, as well as on bacteria. The phagocytic index (the relation between the number of leukocytes and the number of ingested bacteria) obtained with typhoid bacilli exposed for some time to dilute solutions of sodium hydrate has been found to be constantly lower than the index obtained with the same bacteria not so exposed. The lowering of the phagocytic index obtained in such instances is to some extent proportional to the concentration of the alkaline solution employed, such lowering, with respect to the normal, amounting to about 70% when a solution of sodium hydrate of 1:50 is employed, to 30% with a solution of 1:400, and to about 10% with a solution of 1:1000. The effect of the alkali on bacterial protoplasm is most intense during the first hour of exposure, and diminishes gradually thereafter.

Serum alkalinized to a point equivalent to 1:50, 1:100, or 1:1000 sodium hydrate solution exhibits a constant diminution of its opsonin content. The lowering of the phagocytic index resulting from such  
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alkalinization is proportionate to the concentration of the salt employed and to the duration of the exposure; however, this reduction is less marked than that obtained in reactions where either bacteria or leukocytes were employed which had been previously exposed to the action of alkaline solutions.

Spontaneous phagocytosis, i. e. independent of any action of the opsonins, is markedly diminished in leukocytes previously exposed to the action of alkaline solutions, amounting in 24-48 hours to only about 50% of the spontaneous phagocytic properties of normal white cells. When using a solution of sodium hydrate of 1:50 phagocytic activity reaches its minimum after 6 hours and disappears completely after 24 hours' contact between leukocytes and the alkali. However, normal leukocytes not exposed to alkali, and kept at room temperature (15° C.) for a similar length of time, exhibit fewer phagocytic properties than leukocytes exposed to weak alkaline solutions, say 1:500 or 1:1000; this may be explained by the fact that the dilute alkali prevents the onset of autolytic processes — of acid nature — which usually occur in cells kept for some time outside the body.

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(1e—61)

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**Further Experimental Studies on Immunization Against *Bacillus Dysenteriae* (Shiga) and Its Toxins.**

*S. Kanai, Brit. J. Exper. Path., London, 3:158, June, 1922.*

The main object of these experiments was to determine the degree of local immunity in the intestinal mucosa produced by the ingestion of dysentery bacilli. The experiments were performed on rabbits and were unsuccessful for 2 reasons: (1) no strain of *B. dysenteriae* (Shiga) was found which, when inoculated into rabbits, gave rise to intestinal lesions to the exclusion of other pathologic changes; (2) all attempts to separate endotoxin from exotoxin were fruitless. Kanai observed that the toxin of *B. dysenteriae* (Shiga) affected principally the central nervous system (medulla and spinal cord) in rabbits and acted upon the capillary circulation generally with the production of congestion and hemorrhage in the various viscera.

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(1e—62)

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**Immunity in Experimental Pneumonia.**

*Paul F. Clark and Eleanor J. Murphy, J. Infect. Dis., 31:51, July, 1922.*

This investigation was undertaken to find out whether the frequent recurrences of pneumonia are due to the nature of the pathogenic organism or to some property peculiar to the lung tissue. Experimental pneumonia was produced in rabbits, not with the Gram positive pneumococcus, but with the Gram negative *Bacillus typhosus*, which commonly induces a persistent immunity of a marked degree. The virulence of a stock culture of this bacillus having been raised by animal passage in 2 strains, the one intratracheal and the other intravenous, 2 groups of rabbits were injected by these 2 routes. The intratracheal group consisted of 10 animals, 5 of which died within 4 days, all with early pneumonic lesions and positive blood cultures. The 5 surviving animals

also developed a definite pneumonia with typical symptoms and areas of consolidation, but gradually recovered. For intratracheal injections, 4 cultures were used, a dose which was less than half the minimum lethal dose determined in the preliminary titration. The intravenous group (9 animals) were injected with  $\frac{1}{8}$  of a culture, the minimum lethal dose previously determined being 1 culture. Of this group also 5 animals survived; 2 died within 24 hours, with positive blood cultures; 2 others died of intercurrent infections.

Coincidentally with the recovery of the surviving animals, specific agglutinins were found in the blood. The composite agglutination curve of the intravenous group reached a higher level (1:3440) than that of the intratracheal group (1:1185); but the peak of the curve was reached in both groups on the same day, the eighth following the injection of the bacteria. The failure of attacks of pneumonia to produce any considerable immunity is probably due, therefore, to the nature of the organism causing the disease rather than to any peculiar properties inherent in the lung tissue. Blood cultures were uniformly negative in all of the nonfatal cases. The blood counts made were too few to permit of definite conclusions, but were suggestive in various respects. The fact that by the intratracheal route the animals withstood many fatal doses, as measured by intravenous tolerance, demonstrates once more the relatively greater resistance of the body when subjected to attack through the lung tissue.

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(1e—63)

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#### **Pneumococcus Infection and Antipneumococcus Vaccination in Guinea-Pigs.**

*L. Gheorghiu, Clujul med., 3:119, April, 1922.*

In November, 1919, the author observed an epidemic among his guinea-pigs that decimated the animals. The pregnant animals died first after abortion from peritonitis, next the young died, and then the older animals, with symptoms of septicemia. Direct examination of the pericardial, pleural and peritoneal exudates, as well as of smears from the organs, showed the constant presence of a Gram positive, encapsulated, nonmotile diplococcus without cilia or spores. This diplococcus could easily be isolated and cultivated. On simple gelatin it grew rapidly in the thermostat at a temperature of 35° to 38° C., also on gelatin that was covered with a layer of erythrocytes or animal serum, and its growth was especially abundant on a mixture of joint fluid with gelatin. In simple bouillon to which a little serum, blood or ascitic fluid was added, it also grew rapidly, caused turbidity of the medium, and after a few days there was a whitish-gray precipitate. It coagulated milk and did not grow on potato. It fermented levulose, glucose and lactose, and to a lesser degree saccharose. Milk serum to which litmus was added was turned red by the diplococcus in 2 or 3 days. If mice were inoculated with the culture they died in 8 to 12 hours of septicemia. Guinea-pigs remained alive, or if they died it was only after 7-12 days. On intraperitoneal inoculation guinea-pigs died of peritonitis in 24 hours. If cultures were rubbed into the mucous membrane of the nose or pharynx of guinea-pigs they died of pneumonia. If the food of guinea-pigs was sprinkled with the cultures they

died of pneumonic infection. In treating the disease the author used gelatin cultures of serum of a guinea-pig that had died of pneumococcus infection and after 12 hours diluted it in physiologic salt solution in the proportion of 1:10, inactivated it at 60° C. for half an hour, and then injected it subcutaneously into the thigh. To young animals he gave 0.05, to older ones 0.1 c.c. After 5 days the young ones were given another dose of 0.1 and the adults 0.15 c.c., and after 5 days more the young ones 0.1, 0.15, and the old ones 0.25 c.c. On the following day the animals were cured. There is a great similarity between this pneumococcus and that of man.

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(1e—64)

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**Hollaender's Test for Determining Immunity Reaction in Tuberculosis.**

*B. Salkin, Haematologica, Naples, 3:300, May, 1922.*

In performing Hollaender's test with a phenolated saline solution of tuberculin and the serum of various animals (man, horse, ox, dog, fowl, rabbit, pigeon), the globulin content of which is definitely known, the author noted that the reaction is more intense where the globulin content is high, being much less marked or even totally absent where there is a very low or practically no globulin fraction. These findings confirm the hypothesis advanced in a previous communication that Hollaender's test is a physicochemic reaction determined by the amount of globulin in the serum.

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(1e—65)

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**The Antigenic Value of Tubercle Bacilli and Other Bacteria Cultivated in Egg Medium.**

*A. Urbain, Ann. de l'Inst. Pasteur, Paris, 36:528, June, 1922.*

For this study, human, bovine, avian and piscine tubercle bacilli, 5 paratubercle bacilli, diphtheria and subtilis bacilli, and staphylococcus and streptococcus were grown in Besredka's egg medium, 50 c.c. of which was placed in each Roux dish. The antigenic values were determined with antituberculous horse serum and with human serums derived from tuberculous patients. The resulting values differed. The human tubercle bacillus was by far the most active. The activity of the diphtheria bacillus was comparable to that of certain paratubercle bacilli and bacilli of ovian tuberculosis. *B. subtilis*, staphylococcus and streptococcus had no antigenic value. Four days' growth produced the most active antigens. The liquid part of the culture became more active with age. Inactive at first, it may become very active in a few weeks. Egg antigens may be quickly and easily prepared, and keep satisfactorily for at least 15 months.

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(1e—66)

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**Fixed Rabies Virus of Exclusively Cerebral Potency.**

*Vittorio Puntoni, Ann. d'igiene, Rome, 32:253, April, 1922.*

The author has observed and studied a fixed rabies virus which has lost its potency when injected subcutaneously or even intravenously, but retains it with full effect when administered into the subdural space or intracerebrally. This virus is of the type prepared for antirabic treatment by the Antirabic Institute in Rome and is the original Pasteur

virus, counting, to date. 1850 transplantations through rabbits. Until 1919 the virus still possessed some relative subcutaneous potency, killing about one-fourth of the albino rats inoculated under the skin, and had an absolute lethal virulence when injected intravenously into the rabbit. a virulence which it has gradually lost since. The condition cannot be explained as being due to an attenuation of the virus, since its potency when administered subdurally remains uniformly unaffected, with the same period of incubation and the same certainty of death.

This loss of paracerebral potency is ascribed by the author to a variation or change occurring within the virus, which has led to a complete adaptation of the latter to the central nervous system with loss of affinity for the peripheral nervous terminals. With respect to human vaccination, it appears that such biologic modification, occurring so suddenly in the Roman virus, cannot cause any dangerous consequences. As a matter of fact, among nearly 800 vaccinations effected in the Antirabic Institute in Rome in the year when the special modification of the virus was discovered (1921) there was not a single case of death from rabies during the antirabic treatment, and no case of death has so far been discovered that has occurred after completion of treatment. On the contrary, the complete harmlessness of the fixed virus when administered subcutaneously has, during the year just passed, led to an intensification of vaccine treatment.

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**Absorption of Tetanus Toxin by the Intestine.**

*W. Dietrich, Klin. Wchnschr., Berlin, 1:1160, June 3, 1922.*

Besredka obtained very high immunity in rabbits previously treated with bile that received killed bacteria by the oral route. Author obtained the same results with this method but the experiment failed immediately when he worked with parasites of the pig. The demonstration of a considerable agglutination titer in animals treated in this way speaks against Besredka's assumption that it is simply a matter of pure tissue immunity. It is a genuine humoral immunity and the bile only favors the absorption of the antigen from the intestine. It was attempted to support this assumption by causing absorption of tetanus toxin from the intestine after giving bile to mice. Author succeeded in causing absorption of considerable quantities of toxin from an intestine previously treated with bile. This could not be done with a normal bowel. Diphtheria antitoxin was given to rabbits in order to determine the quantity which may be absorbed. The quantities absorbed in the intestine were examined according to the intracutaneous method of Römer. In older animals one five-thousandth of the antitoxin units given was found in the serum while younger animals showed one ten-thousandth at the most with or without previous bile treatment. Bile and the bile salts help in the absorption of the larger molecules, a thing not previously understood.

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(1e—68)

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**Purification of Cow-Pox Lymph.**

*J. W. Janzen and L. K. Wolff, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:2252, June 10, 1922.*

It is very difficult to free the calf lymph from the prejudicial micro-  
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organisms which are always found in that fluid. The staphylococci are the most frequent of them and numerous attempts have been made to eliminate them from the lymph.

The glycerin employed for the conservation of the lymph has a purifying influence upon the lymph, although the antiseptic power of glycerin is not very considerable. Twort, Bordet and Ciucca have found in the lymph a substance which attacks and destroys the colonies of staphylococci and which is probably identical with d'Herelle's bacteriophage. Janzen and Wolff have made experiments in order to see if the action of the bacteriophagous substance could be proved, and if the self-purifying influence of the lymph was a real fact. Their results show: (1) glycerin alone is less active than glycerin with the bacteriophagous substance; (2) the lymph itself is bacteriophagous; (3) it is probable that the disappearance of the staphylococci is due to the bacteriophagous power of the lymph; and (4) the addition of the bacteriophagous substance (chiefly of one active against staphylococci) is the best means to purify the lymph.

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(1e—69)

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#### **Studies on the Formation of Bacterial Toxins. I. Staphylo- lysin.**

*L. E. Walbum, Biochem. Ztschr., Berlin, 129: 367, May 3, 1922.*

Formerly the preparation of a bacterial toxin presented great difficulty because the individual factors that favor the production of an adequately active toxin were not known. It is now known that the pH of the nutrient medium is of determining importance. The factors involved in all biologic processes — temperature, time and pH — were investigated with reference to the growth of staphylococci and to their influence on lysin action and on the preservation of the lysin formed in cultures. Further, the significance of the composition of the medium was examined, as magnesium salts possess pronounced activating properties. Electrometric pH measurements in liquids having pH lower than about 6.0 always proceed smoothly; in neutral or alkaline media and cultures they are frequently impracticable. The cause lies in the formation of volatile substances (ammonium-sulphur compounds) during warming. Electrometric measurements agreed with colorimetric estimations, Sörens' standard solutions and the various temperature corrections being employed. On warming the bouillon pH diminishes with rising temperature; it is greatest in the most alkaline mixtures and lessens gradually with decreasing alkalinity. Summarizing the various experimental results it is seen that these alterations of pH with temperature are the same for peptone-bouillon preparations prepared at different times. This is the case too with bacterial cultures in peptone-bouillon (staphylococci and diphtheria bacilli) examined at different developmental stages, as also with their filtrates (i. e. toxins). This behavior is of value, as it permits, for instance when the pH of a bouillon at 18° is known, the amount by which this bouillon's pH is displaced on being warmed or cooled 1° to be read off by means of a curve on which the displacements of pH for 1° are entered as ordinates and the corresponding pH in the investigated fluids at 18° as abscissas.

The experiments show that the optimum pH for growth lies at

about 6.50, which is the same at all temperatures between 10.5° and 48°. The temperature optimum for growths lies at 34-36°. All cultures tend to maintain a concentration of pH=8 to 9. Lysin formation in the cultures proceeds chiefly as a rise followed by a fall, but the rise as well as the fall takes place more quickly with increasing temperature. No lysin or only trifling amounts are found in cultures of the highest alkalinity; only in cultures whose initial pH is about 8-9 do larger amounts of hemolysin occur; the lysin content increases with the bouillon's acidity and is greatest with the most acid. The concentration most favorable for the preservation of staphylolysin lies at pH 6.0. The time optimum for lysin formation depends on the temperature as well as on the bouillon's initial pH. It sets in earlier with increasing temperature up to about 40°, at which the lysin curve attains its optimum after 2 or 3 days. By adding buffers (phosphates) pH fluctuations in the cultures were largely prevented, 2-4% salt being required. In nonalbuminous media no growth of staphylococci took place; on addition of 1% peptone, growth was obtained. The experiments showed further the great importance of  $K_2HPO_4$  for growth and of  $MgSO_4$  for lysin formation. As regards the bouillon the most favorable meat concentration was found at 25% (i.e. 250 gm. meat to 1 liter of medium), as the amount of lysin formed becomes less with larger as well as with smaller content of meat extractives. Peptone concentration (0.0-3%) does not apparently play any considerable part in the amount of lysin formed; the velocity of production is greater in cultures with little than in those with much peptone; on the other hand, the curve falls sooner. The culture's sodium chlorid content is of the utmost importance for the formation of lysin, as the latter diminishes gradually and regularly with increasing salt content. As pH is usually increased by sterilization in autoclaves the medium must not be employed until its pH has been again tested and its reaction has been corrected by means of acid or base. Having regard to the observation that  $MgSO_4$  promotes lysin formation a series of experiments were carried out on the significance of the presence of other metallic salts in the cultures during growth. These experiments demonstrated that each of the investigated metallic salts either promotes or arrests lysin formation in any concentration, but no uniformity seems to exist within the different groups. Salts of magnesium, nickel, manganese and platinum promote lysin; calcium salts arrest strongly and in slightly larger doses (0.1% of a 1/1 molecular solution) they abolish the formation of lysin entirely.

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(1e—70)

**The Effect of Peptone upon the Toxigenic Property of *Bacillus Diphtheriae* No. 8.**

*Harriet Leslie Wilcox, Am. J. Pub. Health, 12:608, July, 1922.*

The strain of *B. diphtheriae* used in obtaining a potent toxin, called No. 8, was isolated in 1895 and so stable have been its toxigenic properties that it is used not only in the serum laboratories of the United States but in those of England and Europe as well. Recently, and coincident with the reports from other laboratories, the potency of the toxin produced at the Bureau of Laboratories of New York City has shown a marked decline. In 1916 several experimental preparations

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of diphtheria toxin were made by the method of the Pasteur Institute with the latter's culture of No. 8. The results were so superior to those obtained with Witte peptone broth and Bureau of Laboratories (B. L.) culture No. 8 that in 1917 Martin peptone broth inoculated with the Pasteur culture was adopted for toxin production. Comparative tests of the B. L. culture, designated as Research No. 8, were made with that of Pasteur No. 8 and a second culture obtained in 1919 from the Pasteur Institute. The cultures were transferred 3 times weekly and cultivated under identical conditions. In Martin peptone broth in one test only did Research No. 8 approximate Pasteur No. 8 in its toxic production. Subsequent tests showed a diminution in the toxigenic production by both cultures. In the tests with Witte peptone broth, despite the fact that Research No. 8 had been cultivated in a medium containing Witte peptone since 1895, the toxigenic property was markedly less than that of Pasteur No. 8 and it was also evident that the toxigenic property of the latter deteriorated in Witte broth. The potency of toxins made from Berna peptone broth was irregular but the results with Parke Davis peptone were encouraging. Here again the marked differences in the toxigenic power of the different strains were in evidence. When it was evident that Research No. 8 produced consistently a much lower toxin than either of the other strains, regardless of the length of cultivation in any particular broth, a test was made to see what effect the different peptones had on the toxigenic power of Pasteur No. 8 after its cultivation in the different peptone broths. The cultures which had been grown exclusively in Berna, Martin and Parke Davis peptone broths gave satisfactory toxins in Berna broth, but the culture which had been transferred in Witte broth since 1916 gave a potency of below 1:100. The tests indicate that Witte peptone broth had an inhibitory or destructive influence upon the toxigenic powers of B. L. No. 8 strain, and on that brought from the Pasteur Institute in 1916, but that it had not yet affected the toxigenic powers of that acquired from the Pasteur Institute in 1919. Possibly the different preparations of Witte peptone received in this country since 1913 were responsible for this deleterious effect as Research No. 8 from 1895 to 1913 gave no signs of lowered toxigenic property. Continuous cultivation of a culture of *B. diphtheriae* No. 8 in the same broth as that used for the toxin production is not necessary for obtaining a potent toxin.

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(1e—71)

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**Surface Activity and Toxic Effect of Saponins. Relation between Physiologic Action and Physical Properties.**

*Ludwig Kofler, Biochem. Ztschr., Berlin, 129:64, April 19, 1922.*

Researches were undertaken on the relations between the physio-chemic properties of saponin bodies and their physiologic behavior, in order to ascertain whether any connection exists between their action in reducing surface tension, of which froth formation is also a function, and their toxicity. Such researches are of importance as the individual saponins differ greatly. Thus, guaia-saponin possesses high spumescent power but hardly any hemolytic action. The behavior toward different animal species also varies. Remarkably resistant to saponin solution were crabs, worms, cephalopoda, snails, sea-slugs and tunicata, while all fish exhibited strikingly high sensitiveness toward saponins. For cal-

culating this so-called fish index, that concentration was determined by which the experimental animal is killed in a definite period, namely, one hour. The hemolytic index was determined in the customary manner, employing a 2% suspension of defibrinated human placental blood in physiologic sodium chlorid solution. The reduction of surface tension of the aqueous solutions was estimated with the aid of Traube's stalagmometer and reduced to the normal drop number (water 100). For comparative experiments the following saponins were employed: glycyrrhizin, digitonin, chestnut-saponin, ruman-saponin, sapindus-saponin, I-saponin, primulin, and pure white saponin.

The experiments showed that the hemolytic and fish indexes of the investigated saponins bear no relationship to the stalagmometrically measured surface activity. In the order of their surface tension-reducing effects individual saponins occupy different positions in the series according to the concentration at which the determination was carried out. If the surface tensions are laid out as ordinates and the concentrations as abscissas, the curves of different saponins show points of intersection. The toxicity does not follow these curves; it is independent of concentration, and on comparing 2 saponins, it does not show the reversal, before and after the point of intersection, to be expected on the adhesive pressure theory.

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(1e—72)

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**Colloids, Catalysis, Antigens, Antibodies.**

*M. Nicolle and E. Césari, Ann. de l'Inst. Pasteur, Paris, 36:463, June, 1922.*

In general, the authors' work and conclusions are in accord with those of Duclaux. They here review later work and give a correct outline of their views on unity of the antibodies, which have not been properly represented in previous publications.

Colloids are discussed as physical systems, chemical compounds and surfaces. Gels are solid colloids, sols liquid colloids and hydrosols are so-called "false solutions" of colloids in water. Hydrosols usually leave insoluble residues on evaporation and are considerably altered by freezing. Colloids do not constitute simple physical systems or ordinary chemical compounds. Colloidal particles are composed of "disordered" molecules, which correspond to various chemical entities, and a reagent which produced the substance. The molecule and reagent should be considered as chemically combined. Thus, colloidal copper ferrocyanid consists of a chemical union of one molecule of K ferrocyanid and  $n$  molecules of Cu ferrocyanid. The copper salt is activated by the K constituent. It forms an inert block or granule, collecting as a whole at one electric pole, the free ion of the other portion going to the other pole. The formula is, therefore written  $(n[\text{Cu}_2\text{FeCy}_6]\text{FeCy}_6)\text{K}_4$ .

Adsorption varies within certain limits. Concentration in the adsorbent varies less quickly than that in the adsorbable liquid, and in proportion as the adsorption is energetic. The conditions are comprised in the formula  $C_1 \text{ equals } KC^m_2$ . Here  $C_1$  represents the concentration in the adsorbent,  $C_2$  the concentration of the adsorbable substance in the liquid,  $K$  a proportional factor, and  $m$  an affinity factor, less than 1. If  $m$  equals 1, the formula describes simple solution. As  $m$  diminishes, adsorption becomes typical. When  $m$  is very small, the formula

describes an ordinary chemical reaction. Every chemical reaction is preceded by the formation of addition or accretion compounds. The latter are rarely isolable, but thermic analysis has shown a few. Here molecules are so united as to permit certain atomic exchanges in the final reaction, up to which point conditions are reversible. Adsorption may be conceived as covering a series of associations more and more directed, of which the chemical reaction constitutes the natural termination. Colloidal stability is closely related to osmotic pressure. Greater stability is associated with more minute particles.

Coagulation occurs as soon as the particle ceases to be in equilibrium with the surrounding medium. Large, unstable particles attract small and stable particles, the association assuming the characters of the stable particles, which thus "protect" the larger ones.

The variability of catalytic conditions may be due to innumerable surface and affinity effects. Antigens include diastases or enzymes, toxins and indifferent constituents of cells and fluids which may be termed unspecified antigens. Enzymes must be considered as colloids, catalyzers and antigens, for they act as such. They are doubly specific, as referring to the substances which they transform and to the antibodies created by their action. Toxins are classed with reference to absence of local action (neurotoxins), toxins producing moist eschars and toxins producing dry eschars. Solid toxins are those which remain in the cells or tissues where they are formed. The latter are usually bacteria. No effects ascribable to neurotoxins appear in plants. Toxins appear opposed to enzymes, but the two really form a continuous series, whose extremes are clearly distinguishable. Distinction is very difficult toward the middle of the series. Like enzymes, toxins behave as colloids, catalyzers and antigens, and are also doubly specific.

Indifferent antigens do not act as catalyzers. As colloids, they act through their inert block or granule. Their specificity is simple, and is shown by their reaction with corresponding serums. This property is utilized in the diagnosis of infectious diseases. For the present, antigens, toxins and enzymes may be regarded as colloidal proteins, containing characteristic active constituents which produce catalytic effects. Outside of a certain number of colloidal proteins, no substances having antigenic properties are so far known.

In living tissues, antigens and antibodies do not unite to form visible precipitates, but interaction nevertheless occurs. The compounds become decoagulated, and they and their complements are digested by proteolytic enzymes. Antibodies are apparently differentiated globulins. In general, their structure resembles that of enzymes and toxins. Fixation effects are effects of adsorption, affinity and surface. Complements consist of colloids composed of very small particles. They attach themselves to, and isolate, the antigen-antibody colloids of larger particles, separate them and thus produce lysis, or decoagulation. The essential character of complements consists of the small size of their constituent particles. The site of formation of the antibodies is unknown, but it may possibly be the vascular endothelium. The antipoietic function, shared by all cells, is especially active in some, which have not been determined. The diminution and absence of antibodies in the serum, after recovery, may be only apparent, present methods being imperfect. Immunity certainly seems linked to the action of antibodies.



Hypersensitiveness depends on the principle that enzymes may produce, with nonantigenic substances, effects similar to those which antibodies produce with antigens. However, one of the authors has been unable in over 6 months to sensitize animals to amygdalin, arbutin or salicin, and yet, in the electric sleep of rabbits, arbutin proved toxic during the sleep, harmless to the waking animal. In anaphylaxis, adsorption occurs. Proteins as well as fats are fixed. Complement scatters the particles of the complex, the albuminous portion being attacked by enzymes.

Antigens are modified by antibodies in two opposite ways, coagulation and decoagulation. The authors think that each antibody has but one corresponding antigen. Every antigen excites the production of one specific antibody. The antibody fixes and coagulates the antigen more or less energetically. No further action occurs, unless complement is present, in which case the complex is decoagulated. The decoagulation will be complete in proportion to the feebleness of the preceding coagulation. In itself, an antibody determines neither coagulation nor decoagulation, simply permitting electrolytes to accomplish the former, and complement the latter. Every serum is both coagulating and decoagulating. One of these two properties often dominates, to the exclusion of the other. The reason may be learned by studying the serum of a large number of horses. The single antibody develops more and more, as circumstances permit, the coagulant effect increasing at the same rate. The latter effect is inseparable from the formation of the antigen-antibody complex, which conditions lysis. When a certain point has been passed, the effect inhibits lysis more and more. The dual action of the serum is thus simply explained. For obtaining highly coagulating serums, immunization must consequently be carried as far as possible. This is the rule with antitoxic, agglutinating or precipitant serums. For obtaining lytic (usually antibacterial) serums, the immunization must be more guarded, excessive agglutinative property avoided and the test animal allowed to rest for a time if the lytic property even slightly diminishes.

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### **The Relations of Heterogenetic Sheep Blood Antigen to Other Lipoid Antigens.**

*Kurt Meyer, Biochem. Ztschr., Berlin, 129:188, April 19, 1922.*

As a result of previous experiments the possibility had to be reckoned with that the antigenic lipoids isolated from tapeworms and tubercle bacilli are nothing else than the heterogenetic antigen. Attempts were therefore made to evaluate each of the 3 lipoids (horse kidney cephalin, tubercle bacilli cephalin and tapeworm cephalin) in the complement-fixation experiment against 3 serums obtained by immunizing rabbits with tapeworm body substance, with killed tubercle bacilli, and with horse kidney and which contained abundant complement-fixing antibodies. The experiments demonstrate the dissimilarity of the 3 lipoids and the strict specificity of their homologous antibodies. Each serum gave a positive complement-fixation reaction only with the homologous antigen. No doubts can therefore be entertained regarding the diversity of the lipoid antigens.

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(1e—74)

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**The Relative Value of Human and Guinea-Pig Complement in the Wassermann Reaction.**

*A. F. Hayden, Brit J. Exper. Path., London, 3:151, June, 1922.*

It has been observed that certain active serum methods, in which the serum to be tested provides the necessary complement, give a more delicate test in borderland cases, that is, they give a positive result more readily when only a small quantity of syphilitic antibody is present. In the course of a duplicate series of tests, using an active serum method in one and the full technic with guinea-pig complement in the other, certain observations suggested to the author that the difference might be due to a different combining value of human complement as compared with that of the guinea-pig, with the complex syphilitic antigen plus antibody. To test this hypothesis a series of tests was performed on several batches of serums from hospital and venereal disease clinics, using both the activated and inactivated serums, with human and with guinea-pig complement.

It was found that the fixation of human complement in the reaction is much more complete than that of the guinea-pig and allows of a more delicate test without the use of cholesterinized antigen. Hayden thinks the difference in delicacy observed in the active serum methods is probably due to this greater fixation of human complement, and not to the absence of inactivation of the serum to be tested. He also tested 44 human complements from 44 individuals to see if the hemolytic titer bore any relation to the fixing capacity in the presence of syphilitic antigen and antibody, and to determine whether human complements differed from one another in fixing power as do those of various guinea-pigs. He found that among healthy human complements there is for practical purposes a constant ratio between the hemolytic titer and the capacity for being fixed with syphilitic antigen and antibody. This constant ratio enables the reaction to be standardized, and in this respect human complement is superior to that of the guinea-pig in the Wassermann reaction.

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**Anticomplementary Properties of Human Blood Serum. Observations on the Wassermann Reaction.**

*U. Parodi, Haematologica, Naples, 3:215, May, 1922.*

Active serums kept for some time acquire autonomous anticomplementary properties. Previous heating to 50° or 52° C. is not sufficient to prevent the acquisition of such properties. Heating of the serum to exactly 56° for 1/2 hour fixes the serum in such manner that even after prolonged preservation it cannot acquire any autonomous anticomplementary properties. These anticomplementary properties are acquired by virtue of instability of temperature, and seem to be connected with the solution of the serum globulins. Both Wassermann positive and Wassermann negative serums, if treated with ether, will fail to acquire anticomplementary properties and will retain their respective reactions in Wassermann tests if they are previously heated (inactivated) for 1/2 hour to 56° C.; active serum (heated to 50° or 51° C.), if treated with ether, acquires the property of absorbing complement; this was shown to be true both for Wassermann positive serums

(examined, naturally, after inactivation) and for negative specimens.

The autonomous anticomplementary properties of the serum after treatment with ether are, generally speaking, acquired properties of a thermolabile nature. It is likely that aging of the serum, or the action of ether, causes various changes in the serum globulins of the various serums and leads to the appearance of anticomplementary properties.

This transformation, since it is nonresistant to heat, does not exactly reproduce the syphilitic changes in the serum, which are, on the contrary, thermostable. Only a positive Wassermann obtained with serums heated for  $\frac{1}{2}$  hour at  $56^{\circ}$  C. has value as a specific reaction for syphilis. Active serum may give a nonspecific Wassermann; the instability of its colloidal state and the tendency to undergo changes in vitro demand the utmost care in the interpretation of the results obtained in Wassermann reactions on serums not previously accurately inactivated by heat.

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**On Specific Erythroprecipitins (Hemoglobin Precipitins?).**

*Ludvig Hektoen and Kamil Schulhof, J. Infect. Dis., 31:32, July, 1922.*

Five or six injections of aqueous extracts of red corpuscles of various animals were given rabbits intravenously every 3 days, beginning with 2 or 4 c.c. and increasing by about 2 c.c. each time. The solutions (with 0.9% sodium chlorid) were made so that 50 c.c. contained the extract of the corpuscles in 1 c.c. blood. The tests were made with progressive dilutions of erythrocytic extracts or serum in small tubes. The erythroprecipitins produced with extract of dog, horse, and swine corpuscles proved species-specific as well as cell-specific; those produced with beef corpuscles were apparently cell-specific, but not strictly species-specific. The titer of the antiserums was as follows (figures in brackets refer to the serum and indicate that antigenic elements were present in the latter as well as in the erythrocytic extract): Dog: dog 24,000; horse: horse 40,000; swine: swine 3200; beef: beef 20,000; horse 2000, goat 800, human 800, monkey 800, sheep 800; sheep: sheep 6400 (16), goat 3200; human: human 5000 (32), monkey 3200.

The conversion of the hemoglobin, which is apparently the main precipitinogen present in the erythrocytic extracts, into carboxyhemoglobin, sulphydrohemoglobin or methemoglobin did not affect the specific serum precipitation. Hydrochloric acid was found to destroy the precipitinogenic elements; but with acetic acid, followed by ammonia, splitting of the hemoglobin into hematin and globin was accomplished with preservation of the precipitinogenic elements. The latter remained in the solution after removal of the globin. Injecting rabbits with these globin-free solutions resulted in the production of antiserums fully as specific in reaction as those produced by injecting the original extracts.

Repeated crystallization or treatment with aluminum cream did not affect the reaction of the hemoglobin in any way, the antigen being apparently either closely adsorbed to the hemoglobin molecule or forming a part of it which can be split off by acids. But the treatment of the globin-free solutions with the cream resulted in the complete removal of the precipitinogens, which seem to be protected against this action only when hemoglobin as such is present.

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**The Specific Precipitin Reaction of the Normal and Cataractous Lens.**

*Ludvig Hektoen, J. Infect. Dis., 31:72, July, 1922.*

These experiments with special reference to the human lens in senile cataract, are based on Uhlenhuth's discovery that the lens of different species contains identical antigenic elements—precipitinogens—that are organ-specific, but not species-specific. Hektoen found that the lens solutions of beef, chicken, dog, guinea-pig, horse, human (normal and cataractous), monkey, rabbit, rat, sheep and swine reacted in the same general way with beef, horse, sheep, swine and human cataractous lens antiserums; further, that none of these lens antisera reacted with the blood serum either of the corresponding or of other species represented, and conversely, that no serum antiserum reacted with any lens solution.

Out of 50 human cataractous lens solutions, 8 gave a reaction (in low dilutions) for human serum-albumin. Anticataractous serum gave reactions in higher dilutions of the different lens solutions than anti-beef lens serum, indicating that there are distinct differences between the antigens in beef lens and human lens of senile cataract, or that the solutions of cataractous lenses may contain substances that inhibit the precipitin reaction of antiserum for beef lens. These explanations seem applicable also to similar observations in regard to fetal human lenses. But in 2 specimens of the latter, ordinary antihuman serum showed the presence of species-specific proteins. Studies with monovalent or simple antilens serum might shed further light on questions of this kind.

The aqueous and vitreous humors occasionally contain substances that react with antilens serum. Beef cornea, retina and uvea, however, do not appear to contain any precipitins in common with the lens. Under ordinary circumstances, rabbits produce precipitins that react freely with solutions of rabbit lens in response only to injections of lens of different species and not in response to injections of rabbit lens. But rabbits previously injected with foreign lens material, i. e. rendered allergic with respect to the lens, responded in some instances to injection of solutions of rabbit lens with new production of lens precipitins which act on rabbit as well as other lens solutions.

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**The Action of Hemagglutinins in Vivo.**

*Carlo Sartori, Haematologica, Naples, 3:255, May, 1922.*

Following the injection of a certain amount of agglutinating serum into the blood-vessels, the red cells continue for several days to exhibit the phenomenon of agglutination, which then gradually diminishes in intensity. A previous injection does not interfere with the appearance of the phenomenon of a subsequent one, made several days after the effects of the former have disappeared. The red cells in circulation have the property of fixing the hetero-agglutinins introduced into the blood stream. The effects of agglutination in vitro are certainly retarded by keeping the red cells in motion. The effects of agglutination of anti-hematic sera in vivo is definitely shown not to be prevented by body

temperature, as some investigators have claimed is the case with iso-agglutinins and auto-agglutinins. Within the circulatory system, also, full development of the phenomenon is interfered with by the movement of the blood column.

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### On Isohemagglutination.

*S. C. Dyke, Brit. J. Exper. Path., London, 3: 146, June, 1922.*

According to the hypothesis of von Dungern and Hirschfeldt only 2 agglutinating factors residing in the corpuscles and 2 residing in the serum are recognized. The manner in which these factors are distributed determine the group of any given blood. If the agglutinating factors resident in the corpuscles be denominated A and B, respectively, and the corresponding agglutinating factors resident in the serum A and B, their distribution in the various groups will be as follows: Group I, no agglutinating factors in the serum, A and B in the corpuscles; Group II, B in the serum, A in the corpuscles; Group III, A in the serum, B in the corpuscles; Group IV, A and B in the serum and no agglutinating factors in the corpuscles.

If the above arrangement be the correct explanation of isohemagglutination it is obvious that by saturation with corpuscles it should be possible to remove the agglutinins corresponding to them from suitable serums. The experiments herein reported consisted in the absorption of the 3 agglutinating serums, those of Groups II, III and IV, by the 3 agglutinable types of corpuscles, those of Groups I, II and III. The serums used were from a day to a week old. The corpuscles were collected in 2% sodium citrate solution in normal saline, washed in and suspended in normal saline, a 50% suspension being used. For absorption 5 drops of this suspension were added to 5 drops of the serum to be tested and left standing in the incubator at 37° C. for 2 hours. On completion of absorption the mixture of corpuscles and serum was shaken up and the corpuscles separated by centrifuging. The supernatant fluid was pipetted off and tested as to its remaining agglutinating power by adding 1 drop of the serum to 1 drop of a 1:400 suspension of the corpuscles against which it was to be tested. The 2 were thoroughly mixed with a platinum loop and 1 loopful of the mixture then used to make a hanging drop preparation, which was examined under the lowest power of the microscope. The final reading of the hanging drop preparation was made to the end of half an hour, during which time it was occasionally agitated. The author found these absorption tests confirmed von Dungern and Hirschfeldt's hypothesis as to the distribution and nature of agglutinins and agglutinable factors in the 4 blood groups. He also observed that serums from different individuals of the same group vary in their agglutinating powers. The relative titer of the 2 agglutinins in any given Group IV serum may be equal or very unequal. Serums from different individuals of this group differ greatly in this respect. Corpuscles from different individuals of the same group vary as to their agglutinability by the same serum.



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**A Simple Cross Agglutination Test for Blood Donors, Using Hemolyzed Blood.**

*Norman M. Guiou, Canad. M. A. J., Montreal, 12:488, July, 1922.*

The recent placing on the market by a reliable firm of human Serum II and III makes very easy the procuring of the wherewithal to do the grouping test, and the simple cross agglutination test here described requires no centrifuge, and as a rule no microscope, and can be done by a country doctor in the remotest farmhouse. The equipment necessary is: 1 small vial of sodium citrate solution (3.85%) with a medicine dropper in its stopper; 4 small test-tubes  $2\frac{3}{4}$  in. long; 2 nipples pipets long enough to reach the bottom of the test-tubes; 1 wax pencil; 1 blood sticker (a No. II Hagedorn needle in the stopper of a small bottle of alcohol); 2 slides; absorbent cotton and ethyl chlorid.

The technic of the test is as follows: Two tubes are initialed at the top for both donor and patient. One tube for each party is placed in the back row of a test-tube rack, or in a teacup, and a drop of isotonic citrate placed in each. The empty tubes are placed in front of their respective mates, either in the rack or in a second teacup. Two slides are marked and placed in front of their corresponding tubes. Donor and patient are bled 5 drops into their respective citrate tubes and the tubes gently tapped with the finger to ensure good mixing. If the blood is dark, it should be shaken until it gets oxygenated and bright red in color. A nipple pipet is placed in each tube and almost all the blood in one tube drawn up, the pipet removed from the tube, and any blood on its sides carefully removed with moist cotton. This blood is deposited at the bottom of the corresponding empty tube in front, and the pipet carefully withdrawn so as not to get any blood on the side of the tube. The pipet is replaced in its original rear tube, and the process repeated with the other specimen. The large volume in the bottom of the clean front tube is to be laked. The 2 front tubes are picked up in the left hand, the wax initials being turned to face each other to avoid being rubbed off. The right hand now directs a spray of ethyl chlorid against the lower part of the tube till the blood is frozen through. The snow is now removed with the handkerchief and the tubes held in the axilla to thaw. Even after the first thawing, considerable hemolysis is in evidence, but the process is repeated 3 times to ensure complete cell destruction. If a jet from the ordinary ethyl chlorid tube is used, one should stand in a current of air to avoid feeling light-headed. After the tubes are warmed in the axilla, the contents of each are dumped out on the corresponding slide. This clear hemolyzed blood is referred to as the serum in the test, for simplicity. The pipet from the opposite whole blood tube, which will carry a small quantity of blood on its tip, is now stirred around in each pool of serum, thereby mixing in the opposite cells. The slides may be picked up and rocked a few times when agglutination, if present, will be apparent in a minute or two.

The blood of a prospective donor may be tested out in a few minutes with no unusual equipment save a few small test-tubes and a couple of cut-down urinalysis pipets.

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**Widal Technic Using Sterilized Cultures.**

*Ruth Gilbert and Anna C. Moore, J. Lab. & Clin. Med., 7: 547, June, 1922.*

Since the advantages of sterilized cultures for macroscopic agglutination tests have been so generally demonstrated, it seemed desirable, if possible, to use a killed culture with a simple microscopic Widal technic. Two cultures were accordingly prepared, one a broth culture of *Bacillus typhosus* prepared according to Dreyer's method, and the other an emulsion from agar slants of *B. typhosus* washed off in 0.5% salt solution and killed with 0.1% of commercial formalin. After subculturing daily for 3 days these were found to be sterile. A series of 40 comparative tests was made with the routine Widal technic, using the living 18-hour broth culture and the 2 killed cultures, with discouraging results. Of the 40 tests, 13 (32.5%) gave a positive agglutination with the living culture. Of those that gave positive agglutination with the living culture 61.5% were positive with the killed agar slant emulsion and 23.1% were positive with the killed broth culture.

The results obtained in a second series of tests performed with a Bender strain of *B. typhosus* were even more unsatisfactory than those obtained with the first set of killed cultures. Comparative tests were then carried out with both killed and live cultures, using the macroscopic method, and both were agglutinated by a number of positive serums in final dilutions of 1:50 and 1:100. The agglutination was most definite and clear-cut with the killed agar slant emulsion. Reliable macroscopic tests were performed with killed cultures which had been preserved for almost a year.

If comparable results with the macroscopic method are to be obtained in different laboratories, it may be possible and desirable to have carefully standardized killed cultures prepared at a central laboratory for distribution.

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**An Agglutinating Serum for Certain Strains of Tubercle Bacilli.**

*J. Smith, Lancet, London, 203: 13, July 1, 1922.*

Serums of individuals suffering from pulmonary tuberculosis have the power of agglutinating emulsions of tubercle bacilli. Koch found this to be true also of people under treatment with emulsions of tubercle bacilli, and demonstrated that animals responded to injections of this emulsion by the production of agglutinins which gradually increased in power. Precipitins are also produced. To obtain the serum used in these tests, a rabbit was given gradually increasing doses of an emulsion of a nonvirulent strain of human tubercle bacilli. After the sixth dose the titer of the serum against the homologous strain was 1:1600. The rabbit was then bled. The main difficulty in doing the agglutination test lay in obtaining a homogeneous emulsion, particularly with bovine strains. It was found that the various strains of tubercle bacilli do not belong to one serologic group. Eleven strains were divided into 3 classes: those agglutinated to titer, those agglutinated to a 1:200 dilution of the serum and those not agglutinated by a 1:50 dilution. It has not been determined whether these are really serologic groups.

Precipitins are produced fairly readily during immunization. Both by agglutination and by the precipitin test there is evidence of a group reaction with certain strains of bovine tubercle bacillus.

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**Three Serum Staining Phenomena.**

*H. Dold, Klin. Wchnschr., Berlin, 1:1210, June 10, 1922.*

In order to make the structure and structural changes in the serum visible in an indirect way to the eye Dold added stains and found that thermic influences are manifested in a very visible way in such stained serums. With Nile blue, brilliant pure blue and neutral red it was found that increased temperature did not affect noticeably either the stain alone or the serum alone, but that a mixture of the stain and serum was changed very perceptibly in color by increased temperature. In the same way the changes which the serum undergoes on long shaking can be made perceptible to the eye. By the addition of formalin the serum staining phenomena are greatly inhibited.

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**Surface Tension of Serum. III. Recovery after Lowering by Surface-Active Substances.**

*P. Lecomte du Noüy, J. Exper. Med., 36:115, July 1, 1922.*

This phenomenon of surface tension was studied with fresh dog and rabbit sera by means of physical methods, the advantages of these methods being that they decompose a complex phenomenon into its elements, introduce the factor time and do not depend on such unreliable standards as hemolysis of red cells. Measurements of surface tension of the same layer of fluid were made by means of the du Noüy tensiometer. The surface-active substance used for these experiments was sodium oleate, which, when added to serum under proper conditions, causes an initial drop in surface tension followed by a rise. This antagonistic action of serum to depression of surface tension by the sodium oleate is more potent when the sodium oleate is less dilute, being strongest for the pure powdered substance. Under certain conditions, when the liquid is not stirred after addition of sodium oleate, the rate of recovery is no longer inversely proportional to the concentration of sodium oleate. Stirring produces the same effect as if the solution were more diluted.

Apparently, certain constituents of serum exert an immediate counteracting effect against the surface tension lowering property of sodium oleate. This accounts for the absence of red cell hemolysis in jaundice cases despite the large amounts of sodium glycocholate and taurocholate in the blood stream, an important defense mechanism, inasmuch as a drop in surface tension would be injurious to the red cells. Heat affects this property of serum to some extent. Following the depression in surface tension by sodium oleate, the beginning of recovery is more rapid than with unheated serum, but after 15 to 20 minutes its curve crosses that of the recovery of the unheated sample and remains below the latter.

All these facts may be accounted for by ascribing this phenomenon of recovery, not to a special substance but to the adsorption of surface-

active molecules by the large colloidal micellae of the serum. This is confirmed by comparing curves of recovery with ordinary curves of adsorption. Furthermore, in the absence of a specific substance in the serum, comparable results should be obtained with inert colloidal substances. In view of the fact that the order of magnitude of the phenomenon depends mainly on the size of the particles, a similar but much slower process was observed with solutions of gelatin, egg albumin and gum arabic.

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**The Precipitation of Colloidal Gold in the Cerebrospinal Fluid of Horses with Dourine.**

*François H. K. Reynolds and Harry W. Schoening, J. Infect. Dis., 31: 59, July, 1922.*

In consideration of the campaign carried on against dourine by the Bureau of Animal Industry on the basis of the complement-fixation test for dourine, and in view of the fact that the colloidal gold test has been used with a large degree of success in classifying affections of the central nervous system, the authors thought that the latter test might give results of scientific interest when applied to the spinal fluid of infected horses. They obtained 33 specimens of spinal fluid from horses the blood serum of which reacted to the complement-fixation test for dourine. These fluids were subjected to the complement-fixation test in 3 amounts (0.1, 0.25 and 0.5 c.c.) with an antigen composed of pure trypanosomes preserved in glycerol. Globulin tests were made according to the Ross-Jones method. With respect to the colloidal gold test, 5 reactions were recognized: no change, red-blue, purple or lilac, blue, pale blue, supernatant fluid colorless, precipitation of gold complete.

The results are arranged in 4 groups: (1) Seven horses with clinical evidence of dourine and postmortem findings. Of these 3 were markedly or slightly positive for globulin, and 2 were positive to the fixation test. (2) This group consists of 6 horses without visible lesions whose spinal fluids gave various degrees of fixation; of these, 5 were more or less positive for globulin. (3) This group includes 18 horses without visible lesions whose spinal fluids failed to react to the complement-fixation test; of these, 5 were more or less positive for globulin. All the horses belonging to these 3 groups gave reactions of various intensity to the gold test—in many cases not in agreement with the other tests; the 5 last-mentioned horses gave a rather subdued reaction to the gold test. (4) This group consists of the only 2 horses giving no reaction to the gold; 1 of them showed a trace of globulin.

In the absence of careful study of the spinal cords, no conclusive interpretation of the reactions to the colloidal gold test is possible. In 7 instances the reactions attained a height of 5. Some curves are similar to those in cases of cerebrospinal syphilis (with the peak at about the center of the scale), and some others are similar to those in meningitis, while no reactions of the paretic type were obtained.

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**A Simple Method of Counting the Cells in Cerebrospinal Fluid.**

*Chas. F. Carter, J. Lab. & Clin. Med., 7: 555, June, 1922.*

The diluting fluid consists of methyl violet 0.2 gm., glacial acetic acid  
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5 c.c., and water to make 100 c.c. With a pipette (1 c.c.), accurately mix equal parts of cerebrospinal fluid and diluting fluid (0.5 c.c. of each). Adjust cover of counting chamber and with a fine capillary pipette, allow preparation to flow over both the Neubauer rulings of the Levy counting chamber, using the same precautions as in making blood count. Let settle for 5 minutes for cells to stain and for preparation to become even. Count all cells in the 4 corner blocks of 16 large squares used for counting white blood-cells and the central block of 400 small squares used in the red blood count. Move to the other ruling and repeat the process. The total number of cells counted multiplied by 2 gives the total cells per c. mm. The high dry lens is used because cells can be differentiated from débris and at the same time a differential cell count can be carried out.

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(1e—87)

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**Experimental Anaphylactic Shock Produced by the Respiratory Route.**

*Fernand Arloing and L. Langeron, Bull. Acad. de méd., Paris, 87:604, June 6, 1922.*

Guinea-pigs, sensitized with 0.1 c.c. normal horse serum injected intraperitoneally, were subjected to the action of homologous, heterologous and bacterial proteins and other substances. Normal horse serum was injected into the trachea, sprayed into the trachea and introduced as a dried powder. The result was a chewing movement, shocks, pruritus, panting, defecation, cough, dyspnea, with gradual return to the normal. Liquid egg albumin was injected, and dried egg albumin introduced as a powder, into the trachea. Powdered peptone, and a spray of peptone solution, were thrown into the trachea. The shock symptoms were produced, as with homologous proteins. Dried *Bacillus subtilis* and *B. tuberculosis* produced no shock, nor did powdered starch, gum arabic or talc, but a slight immobility and bristling of the hair occurred 30 minutes after spraying powdered marshmallow. The anaphylactic shock produced in these experiments was general, and not localized in the respiratory tract. The vascular symptoms suggest Widal's hemoclastic shock. Serum produced increased coagulability, lowered blood pressure, peripheral anemia and slight leukopenia in about 8 minutes. Peptone produced the same in 3 minutes. Asthmatic symptoms require a special predisposition, or colloidoclastic diathesis.

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(1e—88)

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**Experiments on the Biologic Differences in the Condition of the Blood.**

*Kj. von Oettingen, Klin Wchnschr., Berlin, 1:1161, June 3, 1922.*

Increased velocity of sedimentation of the red blood-cells is associated with changes in the plasma. These are seen as slighter coagulability, lesser filling and increased lability of the albumin body of the blood plasma. Influences which favor clotting of the citrated plasma show similar differences. Incubation of citrate plasma with the venom of *Daboia Russelli* absolutely prevents clotting with the plasma of the new-born; the plasma of adults is but slightly clotted and the plasma



of the gravid is unclotted. The addition of calcium chlorid to the citrate plasma causes the plasma of the new-born to clot the fastest while normal plasma and the plasma of the gravid shows delayed clotting. The plasma of the gravid is less coagulable than that of the new-born if the plasma be diluted.

The influence of temperature on the plasma coagulation, the fact that increased lability is found also in the serum of the gravid, the stronger agglutinating effect on bacteria, the differences in the hemolytic effect of the serums and the activating effect with cobra venom show that the peculiarities of the serum of the gravid do not depend alone on a quantitative increase of the fibrinogen. Sheep's blood which is not affected by cobra venom is made sensitive to it by heating. The heating of sheep's blood for 30 min. at 50° C. does not lead to a direct sensitiveness but quantitative differences in the effects may be recognized in serum inactivated at 55°. This difference is especially noticed in the very strong activation with serum of gravid women when added to serum of less power, such as normal serum, while it is absent in the serum of the new-born. The various reactions in the blood, aside from the quantitative differences of the various albumin fractions are to be looked for in the variable peculiarities of the physicochemical structures of the blood plasma.

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(1e—89)

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**Refractometric and Viscosimetric Studies of the Blood Serum.**

*Fritz Rohrer, Schweiz. med. Wchnschr., Basel, 52:555, June 1, 1922.*

The principles of the 2 methods used in the examination of blood serum were tested, that is, the method of Reiss of determining the protein content of the serum and that of Naegeli for determining the amounts of albumin and globulin in the serum protein. It is necessary to find out: (1) how large is the refracting part in the nonprotein body in the serum and to what degree is it variable in individuals; (2) how large is the total refraction for 1% serum protein; (3) how large is the specific total refraction for the 2 chief fractions of the serum protein, the serum albumin and the serum globulin; (4) whether the mutual relation of the refraction and viscosity values is the same for the albumins as for the globulins in all individuals, or, if not, to what degree is it variable in different individuals.

From tables showing author's results, he concludes: (1) The refracting part of the nonprotein substance in the blood serum, which is equal to the refracting part of dialyzable substances, is somewhat lower than the value given by Reiss; this is almost attained when the fats and lipoids of the serum are taken into consideration. (2) The specific total refraction for 1% serum protein was found to be somewhat higher than Reiss' value. Reiss' tables were only slightly changed in any field that was of clinical importance. (3) The 2 chief fractions of the serum protein have the same specific total refraction as the total protein. A change in the proportion of serum and protein therefore has no effect on the reliability of Reiss' method. (4) The examination of pure albumin and globulin solutions from a large series of men and cattle confirmed the correctness of the principles of the aforesaid methods for determining the proportions of albumin and globulin in

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the blood serum. The slight variations in the coördination of refraction and viscosity values of pure albumin and pure globulin solutions are probably caused by sources of error in the methods used. In the globulins long keeping and partial drying cause a marked increase in viscosity.

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(1e—90)

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**On the Determination of the Total Oxygen-Combining Power of the Blood in the Van Slyke Apparatus.**

*Christen Lundsgaard and Eggert Möller, J. Biol. Chem., 52: 377, June, 1922.*

In a convenient modification of Van Slyke's procedure 6 c.c. water, containing 2-3 drops of octyl alcohol and 0.3 c.c. of 1% saponin, are run into the apparatus. After the usual evacuation this is drawn down and trapped in the wide branch of the apparatus below the lower stop-cock. The stop-cock is turned and mercury is run very slowly upward through the apparatus in order to collect the film of water left on the inside. The water is then run out of the left side of the upper part. The upper stop-cock is now turned and mercury is run into the bottom of the cup. If any moisture is left in the cup from the introduction of water it is dried by filter paper. Then 2 c.c. blood are introduced into the cup and drawn down almost to the bottom of the 50 c.c. chamber. The apparatus is now shaken for half a minute by hand or for 2-3 minutes by a mechanical shaker. The upper stop-cock remains open. Thereby the blood is saturated. Mercury is again run up into the 50 c.c. chamber collecting the blood at the top. When the blood column reaches the upper stop-cock, this is closed. The stop-cock is now turned so that the previously trapped air-free water is allowed to rise into the chamber. The lower stop-cock is closed and the apparatus turned upside down once in order to mix the water and blood. After one-half minute the blood is laked. Saturated potassium ferricyanid is now added and the determination made as described by Van Slyke in 1918 and modified by Van Slyke and Stadie in 1921. The authors' procedure requires less blood and less time than the original method, and there is no possibility of introducing error by evaporation during the saturation of the blood in the separatory funnel.

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**Acid. Production in Shed Blood.**

*C. Lovatt Evans, J. Physiol., London, 56: 146, May 16, 1922.*

It is evident from existing data that the cause of autogenous acid production in shed blood is to be sought in the formed elements of the blood, and is not due to bacterial action. In searching for its cause it occurred to author that it might be associated with the phenomenon of glycolysis. In the experiments performed samples of human, dog's and goat's blood, respectively, were drawn into syringes containing appropriate anticoagulants. The blood of cats and rabbits was also used. The carbon dioxid contents were determined by Van Slyke's method and in some cases dissociation curves were plotted. The extent of the change, i. e. the reduction in the carbon dioxid capacity of the blood after standing, was noted, as was the effect of temperature. The author

also noted the relation between fixed and free carbon dioxid, the relation between glycolysis and acid production, and the effect of mere lowering of free carbon dioxid on the change. Results show that the fall in carbon dioxid capacity of shed blood is due to a conversion of glucose into lactic acid as a result of glycolysis, and also indicate that the change is greatly accelerated, though not actually produced, by a lowering of the carbon dioxid pressure of the blood. These facts are of importance in all experiments on the carbon dioxid dissociation curve. The change can be retarded by adding 0.05-0.1% sodium fluorid to the blood. Equilibrations at body temperature can then be performed with little change in the carbon-dioxid capacity of the blood.

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(1e—92)

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**On the Hydrogen-Ion Concentration and Some Related Properties of Normal Human Blood.**

*J. Barcroft, A. V. Bock, A. V. Hill, T. R. Parsons, W. Parsons and R. Shoji, J. Physiol., London, 56: 157, May 16, 1922.*

The authors wished to establish, in a number of normal persons, the relations existing between the H-ion concentration (cH) and certain other properties of human blood. The relations established experimentally at 37° C. for the blood of the average normal man, and also the variations therefrom among 10 normal persons were: (1) The relation between plasma -cH (as measured by the H-electrode) and  $p\text{CO}_2$ , the  $\text{CO}_2$  pressure. (2) The relation between  $\text{CO}_2$  pressure and  $v\text{CO}_2$ , volume p.c. of total absorbed  $\text{CO}_2$ . In the average normal man the empirical relation  $\text{cH} = 4.7 \, p\text{CO}_2 / v\text{CO}_2$  is accurately obeyed. (3) The relation between the volume p.c. of absorbed  $\text{CO}_2$  and the H-ion concentration is exactly linear over the range of physiologic importance, having the equation  $v\text{CO}_2 = b \times (10^8 \text{ cH}) + c$ .

In the average normal man  $b = 8.4$  and  $c = 16.6$ , while in normal persons the range of  $b$  is  $\pm 2$ , and of  $c$   $\pm 10$ . The quantity of  $b$  is of great importance, being a convenient measure of the degree to which the blood is buffered. This equation, together with that given in 2, enables one to calculate any one of the 3 relations required. (4) The relation between  $1/K$  and  $\text{CO}_2$ -pressure,  $K$  being the constant of Hill's equation, calculated for  $n = 2.5$ , was not exactly linear, but slightly S-shaped. The authors confirmed the existence of a linear relation between  $\log 1/K$  and  $\log \text{cH}$ . According to Hill's theory  $1/K$  should be proportional to the first power of cH: this is shown to be true if one assume a value of 2.2 for  $n$  instead of 2.5. If  $K_0$  be the value of  $K$  calculated for  $n = 2.2$ , the equation  $1/K = a (10^8 \text{ cH})$  holds, both for the average normal man with  $a = 360$ , and for 9 individuals with  $a$  varying from 316 to 436. The authors discuss the reason why, at a given plasma-cH, the dissociation curves of 2 individuals may be different. They conclude that this is due to a Donnan membrane equilibrium occurring at the corpuscular envelope, differences of basic ion-phosphate ion concentration on the 2 sides of this membrane resulting in inverse differences of H-ion concentration, with consequent differences in the oxygen-dissociation curves.

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**Studies of Acidosis. XVIII. Determination of the Bicarbonate Concentration of the Blood and Plasma.**

*Donald D. Van Slyke, J. Biol. Chem., 52: 495, June, 1922.*

In order to determine the acid-base balance of the blood as previously outlined, it is desirable to ascertain the bicarbonate concentration existing in the blood in the body. This may be done by (a) a gasometric determination of plasma or whole blood bicarbonate or (b) titration of plasma bicarbonate. The author has obtained results by both methods and has tabulated the data acquired. (The article is accompanied by detailed mathematical formulas.)

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**Studies of Acidosis. XIX. The Colorimetric Determination of the Hydrogen-Ion Concentration of Blood Plasma.**

*Glenn E. Cullen, J. Biol. Chem., 52: 501, June, 1922.*

The blood is drawn, without stasis and without exposure to air, into a glass syringe coated with potassium oxalate to make 0.3% and containing mineral oil. Without exposure to the air, the blood is then run into a tube under oil to the complete filling of the tube. A one-hole rubber stopper is slipped into the tube, expelling through the hole the oil that remains over the blood. The hole is closed with a glass plug, the tube is placed in a centrifuge, and whirled. The plug is then taken out and as the stopper is removed from the tube, oil is allowed to run in through the hole in the stopper to cover the surface of the plasma so that it is never exposed to air. The plasma is transferred under oil to another tube; 35 drops of 0.03% phenol-red solution are added to 100 c.c. of 0.9% sodium chlorid solution, freshly prepared from redistilled water; 1-3 drops 0.02 n. NaOH are added to bring this solution to pH 7.4 or 7.5 and 20 c.c. portions are placed in suitable tubes and covered with mineral oil. Other tubes are prepared with 20 c.c. saline solution without indicator. A 1 c.c. portion of the plasma is allowed to run under the oil into the indicator-saline solution and another 1 c.c. portion into the 20 c.c. saline solution. This latter tube is for use with the pH standard in the comparator. A 1 c.c. bulb pipette, graduated to deliver between 2 marks, is convenient. The plasma and saline solution are then mixed by introducing a stirring rod through the oil, and the pH determination is made by placing the tubes in a comparator block, and matching to the nearest standard color tube. It is possible to read to 0.01 or 0.02 pH. The temperature of the solution is determined by inserting a thermometer into the solution immediately after the pH reading. The reading should, if possible, be made at 20° C. The pH observed is corrected to 38°.

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**The Alkaline Reserve of the Blood of Fish in Relation to the Environment.**

*Edwin B. Powers, Am. J. Physiol., 61: 380, July 1, 1922.*

In the author's experiments 5 fish were placed in a live car just off the docks of the laboratory at the Puget Sound Biological Station; (Sec. 1—Page 331)

5 other fish of as nearly equal sizes as possible were placed in a tank, 40 x 11¼ x 16 in. of sea-water through which carbon dioxide had been passed. After 5-7 hours the alkaline reserve of the blood plasma was determined by the colorimetric method described by Marriot, the blood being obtained from the caudal artery by severing the tail. The difference in the shade of the color of the dialysate solutions of the 5 fish kept in the live car was indistinguishable. Size had no effect on the alkaline reserve of the blood plasma. All showed an alkaline reserve as indicated by a pH of 7.65. The 5 experimental fish showed an alkaline reserve as indicated by a pH of 7.83-7.87. These facts indicate that certain nonmigratory marine fishes are able to change the alkaline reserve of their blood to accommodate them to variations in the carbon dioxide tension or the oxygen tension of the sea-water, or both.

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**The Determination of Magnesium in Blood, Plasma, and Serum.**

*W. Denis, J. Biol. Chem., 52:411, June, 1922.*

Bell and Doisy have previously described a colorimetric method for the determination of small amounts of phosphate by means of molybdic acid, which appears to possess advantages over the nephelometric method of Denis. The latter has applied the colorimetric method to the determination of magnesium ammonium phosphate with uniformly good results, the tabulated results showing an average recovery from serum, plasma and blood of 96%.

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**The Use of Open Delivery Tubes in the Distillations when Determining Urea and Nonprotein Nitrogen in Blood.**

*Guy E. Youngburg, J. Lab. & Clin. Med., 7:552, June, 1922.*

In the distillation of ammonia formed, either in the urea determination or in the determination of nonprotein nitrogen after micro-Kjeldahl digestion, it is not necessary that the delivery tube shall dip into the acid solution in the receiver, provided the latter be kept at or below room temperature. This is accomplished by placing the receiver in a beaker of water. The condensation of the water vapor is complete and since only small quantities of ammonia are involved there is no loss. The procedure followed was that of Folin and Wu except for the following: In the open method the delivery tube reached only near (1-2 cm. above) the surface of the acid solution in the receiving tube (200 x 20 mm.) which in turn was placed in a 600 c.c. beaker nearly full of tap water. The water submerges the tube about two-thirds of its length. Since this tube was not to be slipped off from its rubber stopper, which contains a slit, the total distillation period was, as prescribed by Folin and Wu, 5 minutes.

Kjeldahl distillations are known to offer the difficulty that the receiver contents are often sucked back into the distilling liquid. Open distillation overcomes this difficulty. The same principle cannot be applied to macro-Kjeldahl distillation because too large amounts of ammonia are involved and more or less nitrogen is lost. Author has found that ordinary paraffin oil should not be used in preventing foam-



ing during distillation. An especially purified paraffin oil, such as is sold for internal use (American oil of Parke, Davis & Co.), should be employed. Such oil is perfectly colorless and water clear and none distils over.

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**The Determination of Globulins in Blood Serum.**

*R. R. Henley, J. Biol. Chem., 52:367, June, 1922.*

(1e—98)

The author describes 2 methods for the determination of globulins in blood serum. For the first method 2 determinations are required: total nitrogen and nonglobulin nitrogen. The first is ascertained by using a 5 c.c. portion of the serum, and is expressed in grams of nitrogen in 100 c.c. serum. In removing the globulins from the solutions for the second determination 60-70 c.c. of a saturated magnesium sulphate solution are added to 10 c.c. serum contained in a 100 c.c. graduated flask and the contents thoroughly mixed by rotation. Agitation, which produces foam in protein solutions, is to be avoided. Then 12 gm.  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  are added to complete the saturation, and the flask is allowed to stand, with intermittent rotation, until the crystals have dissolved, when the contents of the flask are diluted to the 100 c.c. mark with a saturated magnesium sulphate solution. After standing over night, the contents of the flask are filtered, a 20 c.c. portion of the filtrate, which should be water-clear, is taken and the nitrogen determined by the Gunning method, using a reduced amount of  $\text{K}_2\text{SO}_4$ . The quantity of nitrogen found, of course, represents the quantity of nitrogen present as nonglobulin nitrogen in 2 c.c. serum, and is calculated to grams per 100 c.c. serum. The total nitrogen found, less the nonglobulin nitrogen, represents the globulin nitrogen. The factor 6.3 is used to convert the globulin nitrogen to globulins, and the results are expressed in grams of globulins per 100 c.c. serum.

In the technic of the second method, in which the globulins are determined by direct weighing, 90 c.c. water are added to 10 c.c. serum contained in a 400 c.c. beaker. After stirring 100 c.c. saturated solution of tested ammonium sulphate are added, with constant stirring. The beaker is covered with a watch glass, allowed to stand until the globulins separate into thick masses, usually over night, and the contents are then filtered through 11 cm. hardened papers, the filtrate being returned to the paper if not clear. The solution either in the beaker, or funnel, is kept covered with watch glasses. After the filtration is complete the precipitate is dissolved, while the paper is in the funnel, with physiologic salt solution. Solution is easily effected. Frequent additions of the salt solution are made but the final volume should not exceed 100 c.c. The solution of the globulins is measured in a cylinder, the volume brought to 100 c.c., and an equal volume of a saturated ammonium sulphate solution added, using the same cylinder to measure the ammonium sulphate solution that was used to measure the globulin solution. The globulins are removed by filtration as before. The globulins from the second precipitation are again dissolved in salt solution, the volume being brought to about 300 c.c. This is brought to a boil, and 2 drops of a 10% solution of acetic acid added if necessary to cause flocculation. Care must be exercised to prevent foaming of the solution as the boiling point is reached.

After standing on a steam-bath until the globulins have separated into a thick flocculent mass, the solution is filtered through a tared hardened paper, any protein remaining adhering to the walls of the beaker being completely removed. In order to remove retained sulphates, the precipitate is washed with hot water, about 200 c.c. being used, and each portion allowed to pass through the paper before the succeeding portion is added. The precipitate and paper are transferred to a tared, aluminum weighing dish provided with a cover, and dried to constant weight, or until a loss of less than 1 mg. is shown after 3 hours drying, at 100° C. As the papers are very hygroscopic the dishes should be tightly covered when removed from the drying oven. The second method requires more time and does not yield quite as accurate results as the other methods; it is useful, however, when a large number of determinations are to be made.

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**Suggestions for the Determination of Uric Acid in Blood.**

*L. Bauman and L. M. Keeler, J. Lab. & Clin. Med., 7:551, June, 1922.*

The standard uric acid solution is replaced with Lovibond tintometer glasses. The Folin-Wu method is followed, using 20 c.c. protein-free filtrate corresponding to 2 c.c. blood. The blue compound is developed in 25 c.c. flasks without the use of sodium sulphite as the glasses are calibrated against the standard uric acid solution of Benedict and Hitchcock. The glasses are placed over the upper end of the immersion cylinders, or prisms, of the Duboscq colorimeter. A red glass (0.4) is placed over the unknown solution and a blue glass (2.9) over the opposite prism, the latter being immersed to the 20 mm. mark in distilled water. It requires a depth of 17.6 mm. of the blue solution obtained with 0.1 mg. uric acid diluted to 50 c.c. to match the colored glasses. The following formula is used to obtain the amount of uric acid (in milligrams) contained in 100 c.c. blood:  $17.6 \div \text{reading of unknown} \div (2 \times 2) \times 100$ . The advantages of the glasses are: (1) They shorten the times of the procedure. (2) They remove the uncertainty arising from the possible decomposition of the uric acid standard solution. The annoying precipitation occasionally encountered in this method may be avoided by the addition of 3 drops of half saturated (in the cold) gum acacia solution, which acts as a protective colloid. A crystal of thymol is added to the gum solution to avoid bacterial decomposition. This device has enabled the authors to perform 300 determinations without a single precipitation.

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**Rest-Reduction.**

*Malte Ljungdahl, Biochem. Ztschr., Berlin, 129:111, April 19, 1922.*

In practice rest-reduction may probably be identified with the reducing capacity of the blood after fermentation has taken place. Two sources of error may, however, arise: (1) The sugar may not be completely fermented. (2) Optically active reducing substances may be

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formed from yeast in the process of fermentation, and become associated with the other substances inducing rest-reduction. The author's experiments show that a decrease of blood sugar occurs without yeast addition. The observed values also show that, in this joint action, the spontaneous glycolytic power of the blood is relatively great when regarded purely quantitatively. Oxalates exert a considerable arresting action on spontaneous glycolysis. Ege's observation that a small amount of fluorin salt greatly impairs fermentation in the blood, and even prevents spontaneous glycolysis, may be explained in a similar manner.

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**Herzfeld and Klinger's Hemochrome.**

*S. Partos, Biochem. Ztschr., Berlin, 129:89, April 19, 1922.*

As Herzfeld and Klinger assumed the so-called hemochrome, which was said to be the mother substance of the pigment of the blood and its derivatives, experiments were undertaken to determine whether hematin and hemochrome are 2 different substances. Both are insoluble in absolute alcohol, soluble in pyridin and both possess the same absorption band in alcoholic bicarbonate solution. The reduced coloring matter of the 2 substances corresponds spectroscopically to reduced hemoglobin.

For further elucidation spectrophotometric investigations of the alcoholic bicarbonate and aqueous alkaline solutions of hematin and hemochrome were carried out. It was shown that light absorption by the 8 alcoholic bicarbonate solutions along the investigated spectrum is identical. The curves of the aqueous alkaline solutions also describe an identical course, and light absorption by an alcoholic bicarbonate solution differs from that of an aqueous alkaline solution precisely to the same degree whether one is dealing with hematin or hemochrome. As it is generally known that hematin solutions possess a varying spectrum according to whether different solvents are employed it is certain that hematin and hemochrome are identical if, though they show a different course in alcoholic bicarbonate solution, in aqueous lye and in aqueous bicarbonate solution, both always show the constant course of light absorption in the same solution. Therefore no coloring matter such as was designated hemochrome by Herzfeld and Klinger exists distinct from hematin.

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**Pigment Metabolism and Regeneration of Hemoglobin in the Body.**

*G. H. Whipple, Arch. Int. Med., 29:711, June, 15, 1922.*

In the contradiction of the usual story of pigment metabolism in the human body, author does not accept as proved that there is any absorption of stercobilin from the intestine. He has published evidence that bile-pigment is not necessarily related directly to destruction of red cells and hemoglobin. Granting that bile-pigment production may be influenced by other factors than hemoglobin destruction, it is absurd to draw conclusions unreservedly as to blood destruction from the analysis of stercobilin—for example, in pernicious anemia. That body protein as well as food factors are concerned in the production of bile-

pigment and hemoglobin is easily established by fasting experiments. It is obvious that disintegrated body cells are used in the upbuilding of hemoglobin and are related to the output of bile-pigment, urobilin, stercobilin and urochrome.

It is well established that the bile-pigment elimination in dogs can be increased by a change in diet. For example, a sudden change from a meat to a carbohydrate diet may increase the bile-pigment elimination more than 50%. Perhaps the strongest argument against the absorption of stercobilin and its utilization in body-pigment construction is the fact that bile-fistula dogs under observation continuously for 2 years or longer show no evidence of pigment lack, no anemia, no fall in pigment production and no reaction whatever to the feeding of bile pigments. Experiments on dogs showed that diets of cooked beef muscle or cooked beef heart were very favorable for a rapid regeneration of red cells and hemoglobin. Cooked liver ranked with cooked muscle. The common food grains (wheat, barley, rice) in the form of cooked bread or crackers did not furnish many factors which promoted red cell regeneration. Full diets of these materials with skim milk effected a slow rise in the level of the hemoglobin and red cells which finally reached normal in from 6 to 8 weeks. More commonly the return towards normal would not exceed 90% of the initial level before anemia was produced (by bleeding). Casein and skim milk could be ranked with food grains as regards their influence on hemoglobin regeneration. As a rule, these foods did not return anemic animals to a high red-cell and hemoglobin level.

A comparison of anemia-fasting experiments with sugar-fasting experiments showed that anemic dogs actually produced more red cells and hemoglobin during fasting periods than during periods of sugar feeding. There was evidence from these experiments that the body conserves with much care the various pigment construction units, which are then recast into red cells and hemoglobin. Iron was inert in secondary anemias. Hemoglobin, given by the mouth, intraperitoneally and intravenously, did influence the curve of red cell and hemoglobin regeneration in a positive fashion, but not to the extent noted with potent diet factors (meat). Arsenic in sodium cacodylate or Fowler's solution was inert in the anemia periods. Lard influenced in no degree the regeneration of red cells and hemoglobin in anemic dogs. Numerous experiments gave no evidence that cod-liver oil influenced blood regeneration. In striking contrast stood the experiments with butter fat, which indicated that under certain conditions some substance in butter fat is able to influence the curve of hemoglobin regeneration and hasten the production of hemoglobin and red blood-cells. The highly pigmented cooked salmon muscle was shown to be inert in anemia experiments. Carrots were inert. Dehydrated celery, parsley and Brussels sprouts were likewise inert. Dehydrated spinach was positive. Fresh beet tops were negative as compared with fresh spinach, which was even more potent than the dried spinach. Canned spinach was somewhat less potent than the freshly cooked material.

Author's conception of pernicious anemia is that there is a scarcity of stroma building material or a disease of the stroma-forming cells of the marrow which limits the output of red cell framework. High stercobilin figures may be a very valuable diagnostic aid in obscure cases

of pernicious anemia, but that these figures indicate a corresponding destruction of red cells may be doubted and an overproduction of pigment may be a safer assumption. The writer looks upon hemochromatosis as resembling diabetes in certain respects—one disease with an inability to handle the carbohydrates, the other associated with abnormal metabolism of pigment factors.

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**Hemoglobin Determinations by the Sahli and Autenrieth-Königsberger Methods.**

*Etsuzo Komiya and Toshio Katakura, Deutsch. med. Wchnschr., Berlin, 48: 591, May 5, 1922.*

In both of these methods the blood to be tested is diluted with 0.1 n. NaCl solution until its color is that of a standard solution of hemoglobin. This involves one source of error owing to the fact that blood mixed with 0.1 n. NaCl solution readily turns darker. This characteristic of darkening is lost if the diluted blood is kept for more than 10 minutes at a temperature of 30° to 60° C., by which procedure it is possible to avoid the considerable variations that otherwise occur.

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**A New Chemical Method for the Detection of Bilirubin with Special Relation to the Study of Bilirubinemia.**

*Giuseppe Sabatini, Policlinico, (Pract. Sect.), Rome, 29: 837, June 26, 1922.*

The reagent adopted by the writer is composed of dilute HCl (12%), with the addition of 5 mg. of NaNO<sub>2</sub> (0.5 c.c. of a 1% solution). To 0.5 c.c. of clear blood serum are added in a small test tube 1 c.c. of distilled water, and 0.3-0.4 c.c. of the freshly prepared reagent. The presence of biliary pigment is immediately revealed by a green color, more or less intense, that soon becomes more marked, and after some minutes commences to change toward a blue; after about ¼ hour the reaction generally pales somewhat and the tendency toward blue becomes more evident. After it has reached this stage the reaction remains visible and unchanged even for several days. The intensity of the reaction is exactly proportional to the amount of biliary pigment contained in the blood. In the serum of normal individuals the reaction is at first wanting; then becomes more or less clearly perceptible as a light greenish tint, the expression of the physiologic bilirubinemia. The blood serum never becomes cloudy.

The advantages of this method are: the great simplicity in the preparation of the reagent and in the execution of the reaction, which does not require any special instrumentarium, not even a centrifuge; the possibility of using the minimum quantity of serum (the reaction is obtained with 0.5 c.c.) to obtain clear results; the carrying out of the reaction directly on the blood serum, and therefore without losing any of the biliary pigment with the precipitate, a matter of considerable importance in quantitative determinations; the presence of hemolysis, so usual in the serum of jaundice, has no effect; the fluid during the reaction remains liquid and therefore permits any later estimation with



the use of colorimetric and spectroscopic methods; the reaction occurs with a green, or greenish blue, that is plainly different from that of the serum, and therefore appreciable in the slightest degrees. Moreover, the green, in its gradations, is particularly adapted for the colorimetric quantitative determinations.

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**A Simple Method of Estimating Bilirubin in Blood-Serum.**

*Herzfeld, Deutsch. Arch. f. klin. Med., Leipsic, 139: 306, May 23, 1922.*

Author showed that besides bilirubin, indol and pyrrol also react with diazonium and likewise produce a red coloration in an acid medium. The test solution employed consisted of 1.0 c.c. of 0.5 gm. methyl-orange in 500 c.c. water and 1.1 c.c. of 2.5 gm. Congo-red in 50 c.c. alcohol, brought up to 500 c.c. with water. The 2.1 c.c. are brought up to 500 c.c. with water and represent a good comparative solution. Pyrrol is found to react 200 times as strongly as bilirubin. For that reason author employs Hammarsten's method. The reagent consists of 1 volume 25% nitric acid and 19 volumes 25% hydrochloric acid. Of this, 1 volume is then added to 4 volumes alcohol (Frisch). From a 0.1% bilirubin solution in 70% alcohol, 0.6% sodium chlorid and 0.3% sodium carbonate dilutions are prepared in the same. The reagent is added in drops until a green coloration is produced. Normal blood-serums contain 1.6-6.25 mg. bilirubin. In pathologic serum over 100 mg., in punctates up to 25 mg. and in the bile about 3200 mg. bilirubin were determined. Luteins and lipochromes were not found.

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**Fibrinolysis. III.**

*M. Rosenmann, Biochem. Ztschr., Berlin, 129: 101, April 19, 1922.*

Fibrinolysin unfolds special activity under optimum conditions but is arrested by a definite degree of acidity and of alkalinity. The substance that is capable of arresting the fermentative action of fibrinolysin is named thromboligin and its preparation was effected from pleuritic exudates. This fibrinolysis-arresting thromboligin is characterized by being precipitable by alcohol and saturation with ammonium sulphate; it is not dialyzable, is soluble in distilled water and is inactivated at 60-65°. This substance may be identical with the substance in serum that arrests fibrinolysis; this however, has not been confirmed so far. Besides being found in serum the substance also occurs in large amount in the lung, thyroid and kidney, in moderate amount in the liver and in very small amount in the cardiac muscle. In pleuritic exudates, particularly in tuberculous patients, thromboligin is greatly increased. Ascitic fluids generally contain less antifibrinolysin. Transudates, cerebrospinal fluid and edematous fluids contain hardly any antifibrinolysin.

The thromboligin content of serum varies in different individuals and in different pathologic processes. If a pleural exudate be inactivated at 46-48° its antifibrinolytic action is increased. In addition to thromboligin a fibrinolytic body was detected in tuberculous pleural

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exudates. Fibrinolysis is arrested not only by antifibrinolysin, but by chloroform, zinc chlorid, ammonium sulphate and acids and alkalies. Chloroform produces clouding of the fibrinolysin solution; ammonium sulphate, zinc chlorid and acids and alkalies precipitate the solution in the presence of salts. A fibrin that was washed a long time under running water dissolved quicker during fibrinolysis as well as during autolysis than a fibrin of precisely the same age washed only slightly.

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**Hematophagy and Hemetaboly as a Normal Function of Various Types of Tissue Cell. I.**

*H. M. Woodcock, J. Roy. Army M. Corps, London, 38:403, June, 1922.*

Woodcock considers that the function of metabolization of blood elements normally is not confined to the macrophages, but is exercised by certain, probably by many, types of tissue cells, not for the purpose of assimilating and making use of the products of digestion for their own growth and multiplication, but in order to elaborate by the utilization of the formed blood constituents (mainly red corpuscles) various substances coming in the category of secretions or excretions, which are requisite for the welfare of the body as a whole. He distinguishes this metabolism of the blood elements, whether it occurs intracellularly or extracellularly, by the term hemetaboly.

Metchnikoff has pointed out that a red corpuscle, in a very early stage of metabolization in a cell, or outside of it, may appear as a colorless, unstaining vacuole; such vacuoles contain in reality hemoglobin in the first stage of hemetaboly. Apparently Metchnikoff did not ascertain that after further alteration, this nonstaining material in the vacuole may subsequently acquire again an affinity for stains, which is the case, e. g. during the formation of platelet granules by the macrophages. A second characteristic observed by Metchnikoff was that where several red corpuscles were in contact or in close proximity there was a tendency for them to lose their distinctness and run together. This is the same phenomenon which occurs in the production of Kurloff's bodies. This mode of behavior may occur on a large scale, extracellularly, and large masses of homogeneous material may be formed. One such instance is the formation of the colloid of the thyroid gland.

Adenomatous tissue was fixed in formalin, and the sections stained with hematoxylin-eosin. A study of these showed in some cases the lining epithelium of 2 fairly large, adjacent tubules practically in contact, there being little or no interfollicular tissue between the 2 epithelial rows. But minute capillaries, containing a few red corpuscles, and apparently isolated corpuscles can always be found. The next most common cellular elements recognizable as such, are the red corpuscles. There are also cells irregularly disposed, which are probably epithelial cells derived from the epithelium of an acinus. In addition, in such an interfollicular zone, the smallest masses of colloid are to be found, and their mode of formation can be studied. Occasionally solitary corpuscles are seen definitely inside a cell; in such a case, the cell nucleus is nearly always crescentic in form, wrapping partially around the ingested corpuscle, which becomes distinctly pale and practically colorless.

It is only in abnormal growth that complete intracellular metabolism is occasionally to be observed. In its earliest recognizable form, the colloid appears as small masses, each approximately the size of a single corpuscle; when these are in contact they soon coalesce. Woodcock considers that these small masses of colloid are formed by the metabolism of the red corpuscles, the hemetaboly being effected by means of a ferment secreted by the nucleus of the epithelial cells in immediate relation, and can find no evidence of the secretion of colloid material in or by the cells themselves. A study of the normal thyroid bears out these conclusion, for all the colloid contains iron as does the hemoglobin of the corpuscles; apart from the chromatin of their nuclei, the epithelial cells of the thyroid do not appear to contain iron. As to how the blood gains access to the lumen of the acini or follicles, there is evidence that the corpuscles pass by diapedesis, either through or between the epithelial cells, into the lumen of the follicle; this is brought about, most probably, by local or temporary increase in the blood pressure. Corpuscles may undergo metabolism in a somewhat modified form both in the epithelial wall and in the lumen itself, but this process does not seem to result in ordinary colloid. (*To be continued*)

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**Megakariocytes (Bizzozzero Cells) and Blood-Platelets.**

*Rinaldo Marchesini, Haematologica, Naples, 3:193, May, 1922.*

Experiments performed by the author (injections of blastomycetes into the femoral vein of a dog, and of defibrinated blood or carmin into the veins of a rabbit), followed by examination of the bone-marrow, showed the essentially phagocytic function of megakariocytes. This phagocytosis may be noticed in two different ways: In the animals injected with defibrinated blood the Bizzozzero cells (megakariocytes), by virtue of the cilia with which they are provided, will engulf all the surrounding red blood-cells, ingesting some of the latter (which, from repeated inclusions, result in the concentric striae or nucleus which is occasionally noticeable) and destroying some others which, not being included within the large cells, will form accumulations of detritus about the megakariocyte. These findings are corroborated by reports of similar observations on the circulating blood of patients suffering from various diseases, on contact with hemohistoblasts, the phagocytic function of which now seems certainly established. When the cells of the bone-marrow are irritated by extraneous material (blastomycetes or carmin) the megakariocytes display their phagocytic function similarly to ordinary phagocytes, taking up these extraneous elements just as the leukocytes do; their phagocytic activity is further demonstrated by the form assumed by the nucleus—which becomes displaced and subdivided into segments, each of which, by the aid of a little cytoplasm, strives to surround the included portions of extraneous matter.

One must regard the blood as containing 3 distinct types of red cells, depending on their resistance: unstable, semistable, and stable. The unstable red cells must be regarded, on account of their liability to instantaneous disintegration, as the precursors of the platelets. These unstable red cells become arrested by the very first obstacle in their way, mass together and become transformed into platelets as a center of

coagulation. In normal coagulation the natural obstacles are the more fragile leukocytes (monocytes, hemohistoblasts) which, by disintegration and adhesion to surrounding tissues, form points of obstruction.

The author further emphasizes the manner in which the unstable red cells suffer various changes leading to their destruction and transformation into platelets. Through examination of the blood of non-mammalian vertebrates (amphibia, birds), having nucleated red cells, he shows that it is precisely the nuclei of unstable red cells which form the accumulations of platelets marking the beginning of a coagulation process. This would point to the conclusion that even in mammals the nuclei of red cells must be regarded as the precursors of platelets, after having undergone some modifications, thus accounting for their "disappearance." The Bizzozzero cells (megakaryocytes), in view of their doubly phagocytic function, are to be regarded as nothing more than elements of equilibrium or balance in the general hematopoietic mechanism.

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**Megakaryocytes in the Peripheral Circulation.**

*George R. Minot, J. Exper. Med., 36: 1, July 1, 1922.*

This paper, one of a series reporting studies on the physiology and pathology of the blood, considers the occurrence of megakaryocytes in the peripheral blood. The author has observed these cells in the blood of myelogenous leukemia patients and also in 2 cases of polycythemia vera, 1 of lobar pneumonia, 1 of Hodgkin's disease, and 1 case of sepsis. Studies were carried out with fresh, vitally stained, as well as with fixed preparations, the cells being readily recognized by either method. The morphology of the blood cells differs somewhat from those seen in the bone marrow, nuclei alone are more often seen entirely or partially stripped of their cytoplasm. The nuclei vary in shape and size, stain deeply, may be fragmented and often present a characteristic spotty internal structure.

Megakaryocytes are most frequently found in the peripheral blood of chronic myelogenous leukemia cases. They were observed in 35 of the 45 cases studied and their presence is indicative of the severity of the disease. The greater number of cells occurred in the more active cases as judged by fever, basal metabolism and the quantitative estimations of immature bone-marrow cells in the blood stream. Increase in blood platelets in these cases was a constant coincidental finding. Many large megakaryocytes were demonstrated in the lungs of 3 of these cases coming to necropsy; capillary embolism having taken place as a result of the enormous number of these cells.

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**Effect of Venous Stasis on the Physiochemic Condition of Blood Corpuscles.**

*Giuseppe Ajello, Policlinico, (Med. Sect.), Rome, 29: 330, June 1, 1922.*

From the author's experiments it is apparent that: (1) The volume of blood-cells increases but little during venous stasis. (2) The water content of all blood constituents diminishes very little as the result of

stasis. (3) The water content of blood serum shows no marked variations. (4) The water content of blood-cells, in the majority of the experiments made, diminished markedly in consequence of stasis.

These findings are exactly the contrary to what one would expect from results obtained with stasis in vitro. Other experiments of the same author show that as between arterial and venous blood, without stasis, there is no difference with respect to water content between serum and cells; on the other hand, comparing venous blood (drawn after stasis) to similar blood obtained in the absence of stasis, one finds a difference in water content not only between total blood and serum, but also between serum and cells.

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**Determination of the Relative Number of Erythrocytes of Different Resistance (Osmotic Resistance Curve) by Means of  $\text{Na}_2\text{SO}_4$ . Influence of Diet on Resistance and Regeneration in Hemorrhagic Anemia.**

*H. J. Hamburger, Biochem. Ztschr., Berlin, 129:163, April 19, 1922.*

Resistance is determined by allowing 0.08 c.c. blood to drop into 3 c.c. salt solution of decreasing concentration and testing for hemolysis after 15 minutes. Intensity of hemolysis is determined by a method whose principle was stated by Arrhenius and Madsen which consists in comparison with a red scale. The latter is prepared by adding 0.08 c.c. blood to 2 c.c. water, complete hemolysis being attained in this way. This degree of hemolysis is referred to as 100. On diluting a part of this liquid with an equal volume of water a solution is then obtained whose hemolytic degree corresponds to 50%. The osmotic resistance curve of erythrocytes that have been washed in salt solutions is termed the primary resistance curve, while the resistance picture of unwashed blood-corpuscles is designated the secondary resistance curve. The experiments showed  $\text{Na}_2\text{SO}_4$  to yield the same results as the theoretically unobjectionable equilibrated Ringer solution in washing as well as for determining osmotic resistance. Experiments were therefore undertaken in this direction which gave the following results:

Solutions of  $\text{Na}_2\text{SO}_4 (+10\text{H}_2\text{O})$ , neutralized when necessary with  $\text{NaHCO}_3$ , are very suitable for washing as also for determining the relative number of erythrocytes of different resistance (osmotic resistance curve). Such curves may be obtained with washed (deplasmated) blood-corpuscles and with unwashed ones. To deplasmate blood-corpuscles they are washed two or three times with 3% isotonic  $\text{Na}_2\text{SO}_4 (+10\text{H}_2\text{O})$  solution which removes from them the lecithin layer adsorbed from the plasma. It is conceivable that the blood-corpuscles pass from the bone-marrow into the blood-channel in this state. These blood-corpuscles furnish the primary resistance curve. Non-deplasmated blood-corpuscles therefore still possess the layer adsorbed from the plasma and their resistance picture represents the secondary resistance curve. Washing with isotonic  $\text{Na}_2\text{SO}_4$  solution renders the blood-corpuscles more resistant owing to loss of lecithin which substance is capable of diminishing resistance. The use of pure  $\text{NaCl}$  solution is not to be recommended for determining the primary and still



less for the secondary resistance curve. The cause lies chiefly in the lyotropic influence which may, however, be neutralized by adding a definite amount of calcium ions, as contained in the serum's ultrafiltrate and also in a Ringer solution whose calcium-ion content is kept constant by means of a suitable buffer system.

The use of ultrafiltrate for resistance determinations can not, however, be entertained in the case of man or even of the smaller animals, as too great an amount of blood is required for that purpose. Further, H-ion concentration must always be kept normal. That is necessary as a loss of  $\text{Co}_2$  from the serum takes place in ultrafiltration. To inexperienced experimenters the use of equilibrated (buffered) salt solutions presents difficulties. But, it has been shown that  $\text{Na}_2\text{SO}_4$  (+10  $\text{H}_2\text{O}$ ) solution yields precisely the same results as the theoretically well-founded invulnerable equilibrated salt solution. That does not apply to potassium oxalate (Widal and his pupils). The use of  $\text{Na}_2\text{SO}_4$  for determining primary and secondary resistance curves enables a number of problems relating to the disintegration and regeneration of blood-corpuscles to be easily investigated. Thus, for instance, it was shown why the addition of lecithin and fatty nutriment is necessary for blood-regeneration in hemorrhagic anemia of rabbits (oats rabbit as against grass rabbit). Further, the employment of  $\text{Na}_2\text{SO}_4$  furnishes simple means for elucidating the question whether alteration of resistance originates from the blood-corpuscles themselves, from the plasma or from both.

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**Do the Erythrocytes in the Circulating Blood in Man Contain Glucose?**

*Martin Brann, Klin. Wchnschr., Berlin, 1:1103, May 27, 1922.*

To settle this question author determined glucose in serum that was obtained without the addition of any substance that inhibited coagulation and also in whole blood by Moeckl-Frank's method; he determined the volume of the red cells with the hematocrite and from these 3 factors calculated the sugar content of the red cells. In 12 cases the red blood-cells contained pronounced amounts of glucose; these included cases in which the amount of plasma sugar was normal, and ones in which it was increased and decreased. He had the same results with Bang's micromethod. The red blood in some cases contained as much glucose as the plasma, but in most cases a little less. As coagulation was prevented, as well as any sort of injury of the red cells, the sugar content of the latter is proved.

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**The Biochemical and Biophysical Relations between the Erythrocytes and the Proteins of the Blood of Normal Individuals at High Altitudes.**

*H. O. Fränkel-Tissot, Schweiz. med. Wchnschr., Basel, 52:613, June 15, 1922.*

Supplementary to the work of other authors showing that there is a true increase of erythrocytes and hemoglobin when there is decreased

oxygen pressure, author points out that new formation of blood does not necessarily occur at high altitudes, but is dependent on the constitution in general and its needs at the moment as well as on the reactive capacity of the blood-forming organs in particular. While under normal conditions no immature products pass into the circulation, the conditions are different in torpid and pathologically changed bone-marrow. In a case of hemolytic icterus for example author saw numerous polychromatic and basophil punctate red cells, which increased in number. In normal material of 9 adults and 5 children he examined especially the mutual relations between the morphologic fraction of the blood on the one hand and the serum fraction on the other. He reports on erythrocytes, hemoglobin, leukocytes and their distribution, the viscosity of blood, serum and plasma, color of the serum, percentage of protein in the serum and the proportions of albumin and globulin.

From these investigations he concludes, in agreement with other authors, that an increase in erythrocytes at high altitudes in the adult depends on the needs of the organism; the same stimulus of altitude that causes a rise in low cells counts may cause a decrease in a high count. The hemoglobin titer sometimes runs parallel, though generally a fall in cell count is accompanied by a rise in hemoglobin value. Young organisms increase their cell count and hemoglobin values more rapidly and to a greater degree. Four of the 5 children observed showed a considerable increase in the erythrocytes and all of them showed increased hemoglobin. The protein values at the close of the experiment were decreased in 4 of the 5 children and in 7 of the 9 adults, and it was found that not only was the protein as a whole decreased, but that also its highly viscous component, the globulin, had decreased. The lowering of the globulin titer seems to be a typical effect of high altitude in adults as well as in children.

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**Rapidity of Sedimentation of Erythrocytes.**

*F. Raue, Arch. f. exper. Path. u. Pharmacol., Leipsic, 93:150, May 2, 1922.*

The effect of different electrolytes and nonelectrolytes in the rapidity of sedimentation was tested in the following manner: 0.2 c.c. blood-corpuscles from defibrinated and centrifuged blood was added to 3 c.c. suspension fluid, then shaken and the rapidity of sedimentation expressed in millimeters of fluid free of corpuscles, was observed. Results showed that in 5.4% glucose solution, the erythrocytes precipitate very rapidly; the addition of 0.0018 gm. NaCl to 4 c.c. glucose solution causes an inhibitory action on the rapidity of sedimentation. Afterward all the other substances were added to the 5.4% glucose and their action tested. Levulose and saccharose act like glucose. Camphor, acetone, chloroform and ether do not affect the rapidity of sedimentation. Methyl alcohol in strong concentration is slightly inhibitory; amyl alcohol hastens sedimentation.

The electrolytes were much more effective. The cations arranged in the order of their inhibiting action on sedimentation in 0.166 n. solution show the following order:  $Mg > Ba > Ca > Na > K$ ; while the anions gave the following results: Iodid and chlorid  $>$  nitrate and

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bromid > acetate > sulphate > citrate. According to the degree of inhibition of precipitation a decreasing series of acids was determined.  $\text{HCl} > \text{HNO}_3 > \text{acetic acid}$  and  $\text{citric acid} > \text{H}_2\text{SO}_4$ . From this series of experiments the conclusion was that as the inhibiting action of electrolytes on the rapidity of sedimentation of red blood-cells is parallel with their swelling action on colloid albumin bodies, there must be one component in them that is responsible both for their action on sedimentation of erythrocytes and on the swelling of the limiting membrane of protoplasm.

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**The Lipolytic Function of the Lymphocytes.**

*L. Aschoff and H. Kamya, Deutsch. med. Wchnschr., Leipsic, 48: 794, June 16, 1922.*

Metschnikoff made a distinction between macrophages and true lymphocytes and pointed out that lymphocytes never incorporate foreign bodies. The only thing that is known of the positive functions of the lymphocytes is that they are involved in albumin digestion. According to Nuna and others it is a question of an acro-albumose in the chemical building up of the granuloplasm that appears in the transformation of lymphocytes into plasma cells. The lymphocytic-plasmacellular reaction can be used in differential diagnosis in contrast with the histocytic one, which is characteristic, for example, of phthisis. Moreover in all chronic destructive processes lymphocytic infiltrations appear.

The authors takes exception to Bergel's assertion that the antigens of lipid character are catabolized by the lymphocytes while the polynuclear leukocytes act against bacteria of inflammation which contain albumin; he also objects to the hypothesis that the macrophages originate from the small lymphocytes. The macrophages, and the histocytes especially, can be stained by various vital stains, while so far it has not been possible to accomplish intravital staining of true lymphocytes or of the plasma cells derived from them. This proves that they are differentiated forms of cells. Moreover in many varied forms of experiments the authors have never seen phagocytosis by true lymphocytes and on this point they confirm the results of Metschnikoff and Ehrlich. They did not demonstrate Altmann's granules which are characteristic in position and form, in the phagocytizing cells; nor did they prove the assertion of a specificity of the lymphocytic reaction to lipid antigens; nor especially a digestive ferment against lipoids characteristic of the lymphocytes.

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**A Plea for the Standardization of the Training for Laboratory Technicians.**

*Garnet B. Grant and Eric R. Wilson, J. Lab. & Clin. Med., 7: 562, June, 1922.*

Technical help in laboratories should have proper training and be required to pass a state board examination and become registered in the state in which they are employed. The proper training of such helpers can hardly be accomplished in less than 2 years. It should include a good working knowledge of inorganic and organic, and of

physiologic, chemistry; a thorough knowledge of bacteriology, as well as protozoology and parasitology; familiarity with all routine work, urine analysis, blood counts, etc., and with tests that are frequently used, but not considered routine; at least 3 months' experience in serology with a knowledge of the theory of complement-fixation tests, and, lastly, a training in basal metabolism and blood chemistry.

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## 1f. PATHOLOGY

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### **Atrophic Forms of Young Human Embryos.**

*Hellmut Becher, Anat. Anz., Jena, 55:417, June 24, 1922.*

Hegar studied in 1863 this question of malformations which develop in early embryonic life from growth disturbances where the malformed embryo is delivered by abortion in the first months of a pregnancy. A greater part of the miscarriages of the first 3 months of pregnancy contain such malformed embryos. Normal embryos which die shortly before abortion show a clearly defined outline of the external form and a sharp surface relief, and the outlines of internal organs can be seen through the transparent skin. In the young malformed embryos all this is lacking. They are opaque, gray-white, sometimes hard, sometimes soft, structures, which, in their appearance, aside from the difference in size, show extensive differences in form from normal embryos.

Microscopic examination shows the following facts with reference to the finer structure of the malformations: According to Giacomini their peculiar tingibility is the first sign of a changed development of the embryonic tissue. Carmin staining is less pronounced and specific. The most striking characteristic is the more or less extensive infiltration of the tissues, depending on the degree of atrophy, with granules or small round cells (wandering cells). There are different theories as to the origin of these elements. W. His believed that they were maternal cells which penetrated the embryo. Giacomini believes that they are cells of the organs changed by the pathologic development and by the death of the embryo into those small round elements. Wallenstein and Engel believe that the round cells come from the blood of the embryo and are changed embryonic blood-cells. The changes in and destruction of tissues are more or less extensive and pronounced depending on the time the embryo has remained in the uterus after its sickness or death. An early degenerative change in the central nervous system is shown by a pronounced swelling of its substance. The varying state of preservation of tissues and individual organs shows that the embryo does not die all at once, but that some of its parts and tissues continue to live and even to develop after degenerative processes have begun in other parts. In contrast to the embryo, the amnion and chorion in most cases show normal or only slightly changed histologic structure. There is a great degree of independence between the embryo and its membranes, to such an extent that after the embryo has died and undergone extensive degeneration the membranes continue to grow for a considerable time and to develop apparently normally. This causes the

abnormal disproportion between the length of the embryo and the diameter of the amniotic sac.

It would be of especial interest to discover the cause and teratogenesis of atrophic malformation: (1) A disease of the maternal organism may cause malformation and death of the embryo; (2) with a normal maternal organism and normal beginning of development, disturbance may take place in the further course of development from a primary injury of the embryo or its membranes; or (3) the reason for the pathologic development may lie in an abnormal condition of the germ cell or the process of fertilization may be defective. In the first and second cases the development of the embryo is completely normal until the injurious factor begins to act, and further growth is disturbed or stopped. Then the tissues die slowly; there is resorption and degeneration of the organs, and round-cell infiltration and malformation of the external form. But if the cause is in the germ cell or in abnormal fertilization, that is, if there is a primary malformation, then the development is defective from the first, there is an incompletely differentiated organism, which soon reaches a standstill in development on account of its defective division and decreased vital energy. Then processes of resorption begin and continue until they cause the expulsion of the embryo which now lies in the mother's body like a foreign element.

When disease of the mother is the cause of the malformation, the disease must have had a lingering course before the expulsion of the embryo, if the latter is to be malformed like the abortive forms. The diseases of the mother are either general diseases of different sorts or local diseases of the uterus, as for example endometritis or anomalies of position. In the first stages of development there are also certain reefs on which development may strike and be endangered. Such for example are the first segmentation, the implantation of the trophoplast, the arrangement of the germinal layers; disturbances of any one of these stages in development may result in general injuries to the embryo. Injuries that begin later cause malformations of individual germ-layer regions or of organs or systems of organs. The striking phenomenon of abortive forms of malformed embryos with continued development of the membranes is explained if there is a primary cause of malformation and the injury is conceived of as having taken place in the process of fertilization or in the first division.

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**Autosite Monster of the Catadidymus Family and Sternodymian Syssomus Group.**

*Pouget, Houël and Ribet, Bull. Soc. d'obst. et de gynéc. de Paris, 10: 841, No. 8, 1921.*

A native Moroccan woman, 23 years old, was sent to the hospital with a diagnosis of twin pregnancy. The uterus was large and tetanized. It became evident that the fetus was a double headed monster, which was easily extracted after section of one of the heads. There was only one placenta. The uterus contained a voluminous interstitial fibroma. This monster belongs to the variety indicated in the title, and will be made the subject of a special report.

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**Xiphodymus Monster. Clinical and Anatomic Study.**

*Audebert and Laborde, Bull. Soc. d'obst. et de gynéc. de Paris, 10:799, No. 8, 1921.*

In a secundipara 24 years old, whose first child was normal, and with no history of syphilis or other diseases, the second pregnancy followed a normal course, without signs of hydramnios. The right head of the monster was first expelled and lived for about  $\frac{1}{4}$  hour. The other head showed signs of life for a while but died 22 minutes later.

The monster had 2 perfectly formed heads and necks, a very wide trunk, 2 arms and 2 legs, a rudimentary arm implanted between the 2 necks behind, 2 spinal columns in the thoracic region united in the lumbar region and forming only 1 sacrum, 1 sternum and 1 thoracic cavity containing 2 pairs of lungs (one of the pair very small), 1 heart with a double arterial pedicle and 2 right ventricles, 1 spleen, 2 digestive tracts independent as far as the duodenum, where there was union between the 2 sets of organs and a single intestine was formed, 1 liver, partly in the thoracic cavity, the diaphragm being incomplete at that point, and 2 aortas. The right aorta was much smaller than the left, and united with the left in the lumbar region after giving off a branch to the right kidney. There were a normal uterus with its adnexa, an unusually long vagina, and perineal orifices nearer to the pubis than normal. The anus was covered by a rudimentary tail with no skeletal frame.

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**Absence of the Suprarenal Capsules with Exencephalus, Polymicrocystic Degeneration of the Kidneys, Inversion of the Viscera and Multiple Malformations of the Limbs and Face.**

*Commandeur, Bull. Soc. d'obst. et de gynéc. de Paris, 10:651, No. 8, 1921.*

A still-born female child, in addition to the malformations mentioned in the title, showed the following abnormalities: union of the eyelids; absence of eye-balls; bilateral harelip; short thick limbs, club-hands and club-feet; polydactylism; spleen located in the right hypochondrium between the liver and diaphragm; apex of the heart turned to the right.

The mother had previously given birth to a normal child. The coexistence of exencephalus and of complete adrenal aplasia is interesting, for other cases of exencephalus are known where the weight of these glands was much below normal. It is suggested that atrophy of the nerve centers interferes with the production of cholesterin by the adrenals, hence their atrophy.

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**A Pseudohermaphroditic Cock.**

*C. J. Parhon and Constance Parhon, Endocrinology, 6:383, May, 1922.*

The subject of this study was described as a hen that crowed and laid eggs but never brooded. At necropsy the testicles were found modified by a pathologic process and possessed two structures having

the appearance of the oviducts in the laying hen. The adrenals, thymus, thyroids, liver and pancreas were normal. In the organ on the right side, the microscope disclosed in places, the structure of the testis of a normal cock, with well developed seminiferous tubules and active spermatogenesis. In other parts was seen a structure characterized by fairly thick, almost hyaline, connective tissue rings resembling those of testicular sclerosis in man. In the trilobed structure on the left side, which was thought to be an ovary, microscopic examination failed to reveal any ovarian characteristics, although 3260 sections were examined. The "oviducts" were, therefore, difficult to account for. The case is to be regarded as one of pseudohermaphroditism.

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**Abnormal Insertion of the Trapezius Muscle on the Clavicle.**

*Henri Marion, Bull. et mém. Soc. anat. de Paris, 92:186, April, 1922.*

The trapezius is normally inserted on the outer third of the posterior border of the clavicle and the adjacent portion of its upper surface. In author's specimen, the insertion, on the right clavicle, includes the outer two-thirds, that on the outer third being normal. The muscle is inserted on the middle third by a tendinous, supraclavicular arch attached to the posterior border. The external end of the arch is inserted at the junction of the outer and middle thirds of the clavicle, the internal end being attached about 1 cm. outside the insertion of the sternocleidomastoid. The anterior muscular fibers terminate in the upper border of the tendinous arch, curving strongly forward and inward, to form a very oblique attachment, which rounds out the postero-inferior angle of the supraclavicular triangle. The lower border of the arch is free. With the middle third of the posterior clavicular border, it forms an elongated oval admitting 2 branches of the supraclavicular branch of the superficial cervical plexus. Extended clavicular attachments of the trapezius, often observed, recall the common origin of the trapezius and sternocleidomastoid. The formation presented by author is rare.

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**A Case of Combined Polydactylism and Brachydactylism.**

*Wilhelm Bjerknes, Norsk Mag. f. Laegevidensk., Christiania, 83: 517, July, 1922.*

A child, born dead in 1918, three weeks before term, exhibited the rare combination of polydactylism with brachydactylism. In 1917 the mother had given birth to an infant in the seventh month, with 6 fingers to each hand, spina ventosa, and other anomalies. Other abnormalities in members of this family had not been discovered. The distinctive feature of this case of polydactylism was the unusual length of the sixth finger, both the phalanges and the metacarpal bone being so well developed that the finger was quite as long as the fifth finger. The polydactylism was bilateral, and each finger lacked one or two phalanges. The double anomaly — an increase in the number of fingers and a reduction of their length — gave the hands a strikingly broad, pawlike shape. One of the feet also showed polydactylism. In the opinion

of Prof. K. Bonnevie this combination of polydactylism with brachydactylism is exceedingly rare, and no record has appeared of a similar case. Dissection showed that the sixth finger was well supplied with muscles and tendons, although flexion of this finger was not as well provided for as flexion of the normal fifth finger. The sixth finger was well supplied with abductor and adductor muscles, and on the right hand could be extended without simultaneous movement of the fifth finger, but on the left side extension of the sixth finger involved extension also of the fifth.

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**The Importance of Potassium Ions and Calcium Ions to Artificial Edema and Vascular Caliber.**

*Rudolf J. Hamburger, Biochem. Ztschr., Berlin, 129:153, April 19, 1922.*

According to Brinckmann's experiments a Ringer solution composed of NaCl 0.7%, NaHCO<sub>3</sub> 0.02%, CaCl 0.02% and KCl 0.01% permits the passage of glucose through the capillary network of the epithelial glomerule. If the composition of the Ringer solution is altered thus: NaCl 0.5%, NaHCO<sub>3</sub> 0.2-0.285%, CaCl (+6H<sub>2</sub>O) 0.04% and KCl 0.01%, glucose is retained. The concentration of calcium ions may dominate the permeability of the epithelial glomerule to such an extent that Hamburger and Brinckmann were able to observe retention of the physiologic amount of glucose even under perfusion of the kidney with a potassium-free liquid. Under these circumstances it seemed of interest to investigate with what liquid the vascular system of a frog should be perfused to avoid the production of edema of the frog's hind-leg, inasmuch as Günzburg found that perfusion with potassium-free Ringer solution did not cause edema provided the liquid had been saturated with oxygen. Accordingly the influence of the potassium-ion and calcium-ion content on the production of edema and and vascular diameter was studied.

The experiments showed that no edema occurs when potassium is omitted in perfusing the frog's leg with salt solution. That, however, demands a definite concentration of calcium ions in the perfusion liquid. A mixture of NaCl 0.6% + CaCl<sub>2</sub> (+6H<sub>2</sub>O) 0.007% is desirable for that purpose. When CaCl<sub>2</sub> (+6H<sub>2</sub>O) 0.006% is employed edema ensues. The same is the case also if to the first-mentioned mixture of CaCl<sub>2</sub> (+6H<sub>2</sub>O) 0.007% 0.01% KCl be added. The cause of this phenomenon must be sought in the abolition of the action of calcium ions by antagonistic potassium ions. Günzburg's observation that no edema results with customary Ringer solution containing 0.02% NaHCO<sub>3</sub> is due to the fact that this liquid contains a large excess of free calcium ions and that potassium neutralizes a part of these surplus calcium ions. Günzburg's prophylaxis against edema is therefore due, not to a specific radio-active potassium effect, but simply to the long-known potassium-calcium antagonism. Direct determinations of calcium ions by Brinckmann and van Dam have shown clearly that the Ringer solution employed by Günzburg contains 35% more free calcium ions than the mixture NaCl 0.6% + CaCl<sub>2</sub> (+6H<sub>2</sub>O) 0.007%, which does not produce edema any more than Ringer solution containing 0.01% potassium. The observed influence of calcium-ion concentration

on the permeability of the vascular wall is attended by an influence on the vascular diameter.

Perfusion of the frog's vascular system with the mixture NaCl 0.06% + CaCl<sub>2</sub> (+6H<sub>2</sub>O) 0.01% induces such powerful vascular constriction that the flow of liquid ceases. If a little KCl be added to the mixture the liquid again commences to flow. This effect is reversible. The parallelism between vascular permeability and vascular constriction is observable, not merely under the influence of calcium ions, but also under that of oxygen. In measuring the dilating and constricting effect of pharmaca after Trendelenburg the proportion of potassium ions and calcium ions in the perfusion liquid should be taken into consideration.

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**An Investigation into the Etiology of Dental Caries: I. The Nature of the Destructive Agent and the Production of Artificial Caries.**

*James McIntosh, W. Warwick James and P. Lazarus-Barlow, Brit. J. Exper. Path., London, 3:138, June, 1922.*

Wishing to determine the degree of acidity required to decalcify tooth enamel, the authors placed normal teeth (free from caries) for 34 weeks into acid nutrient broth of pH values varying from 5-1. The teeth had previously been sterilized in the broth by autoclaving. At the end of the period the degree of whitening or opacity of the enamel was noted. No change was seen in those teeth placed in broths of pH values higher than 4, and only such a minute trace in those in a pH of 4 that it could be considered negligible.

In studying the bacteria responsible for dental caries, incubation broths of varying degrees of acidity were made from the affected parts of carious teeth, and then agar plates were heavily inoculated. The authors found that the carious material selected showed the constant presence of a definite type of bacillus for which they propose the name *Bacillus acidophilus odontolyticus*. Teeth left in contact with pure cultures over prolonged periods showed changes almost identical with those found in natural caries, such as erosion of the enamel with penetration of the dentinal tubules and the formation of liquefaction foci.

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**The Present Status of Cancer Research.**

*O. Lubarsch, Klin. Wchnschr., Berlin, 1:1081, May 27, 1922.*

The biologic significance of a tumor may be determined not only by the nature and rapidity of its growth but by its localization, for instance a fibroma of the spinal meninges may cause death. Histologically benign tumors may give rise to metastases, which have been observed not only in enchondromas but even in a case of lipoma. Though there is a direct relation between abundance of cells and variety in cell growth and consequently malignancy, yet the abundance of cells and immaturity of cells and tissues is really only a manifestation of the rapidity of growth. Even benign tumors when they grow rapidly may contain immature areas, and on the other hand malignant ones may contain fully matured cells and tissues. Absolute morphologic specificity

has thus far not been demonstrated for tumor cells, even for malignant ones; chemical and biologic differences are at most of the quantitative nature. All these facts argue against Hanseemann's theory that the foundation of tumor formation is a primary fundamental change in the nature of the cells.

It is possible to produce cancers at any desired point on the skin of rats and rabbits with great regularity by painting with tar. These significant results argue against any individual or local predisposition and against the parasitic theory. The further fact that the first symptoms of tar cancer develop after the irritant has acted for months indicates that the cancer problem is not one of specificity, but one of quantity; that it is not a question of the specificity of the stimuli but of their strength and the duration of their action. This conception is supported by spiroptera cancer in the stomach and tongue of rats and by the development of liver sarcoma after feeding with a tapeworm from cats. Cohnheim's theory that cancer development is to be attributed to abnormal cells from embryonic life, cannot be reconciled with these experimental results. There is a fundamental difference between tissue malformations based on developmental or embryonic disturbances and tumors arising from completely normally developed and normally placed cells, with reference to the vital question of why they grow independently and anarchistically. A general explanation of the characteristics of growth is not possible by Cohnheim's theory, for if it were it would not be possible to produce cancer in mice in 100% of the cases by painting with tar.

An argument against Hanseemann's anaplasia theory is furnished by the fact that in the earliest stages of mouse cancer there is no anaplastic cell change; anaplasia is at most only a manifestation of incomplete cell maturity caused by excessive rapidity of growth. But the experiments are a strong support for Virchow's theory of irritation. The subepithelial loosening of the connective tissue is of great importance for the penetration of epithelial cells into the deep tissues, which corroborates Ribbert's cancer theory. In spiroptera cancer in rats inbreeding is a predisposing factor; such factors may also be of importance in human pathology.

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### **The So-Called Basal Cell Cancer.**

*Siedlecka, Polska gaz. lek., Cracow, 1: 489, June 11, 1922.*

In the year 1090 Krompecher described a special form of carcinoma as basal cell cancer. Krompecher's cancers are carcinomas which arise from proliferation of the deepest epithelial cell layers. There is a proliferation of these cells downward; they penetrate the skin and glandlike structures develop. Author examined a case of this kind of cancer. The new growth was in the external ear of a man of 56. The hard tumor was covered with normal epidermis. The cylindric cell layer of the epidermis grew into the deep tissues and was arranged in bands and nests with numerous flask-shaped and club-shaped plugs. Within the band these cells lost their oblong form and assumed round and oval forms. Their nucleus was dark, but sometimes hyperchromatic.

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**The Influence of the Characteristics of the Tissue in the Production of Experimental Cancer with Tar.**

*Gustave Roussy, Bull. Acad. de méd., Paris, 87: 617, June 6, 1922.*

The production of cancer is now considered related to precancerous states and a number of causes may be present. Experimental cancer may be induced by parasites, the x-rays, tar, etc. A previous series of experiments with tar has been already reported. The author here discusses the results occurring in a second series of 60 animals (adult mice). A line of tar was traced every 2 days from the nucha to the tail, the direction of the application alternating. In the 60 tests, there resulted 23 cancers, 16 benign tumors, 14 negative tests, and 7 toxic deaths. In 19 tests the tumors were multiple, in 20 single. The recorded findings were those present 240 days after beginning the tests.

The effects of the tar thus varied considerably under identical conditions. The fact brings out the importance of individual susceptibility and the resistance or receptivity of the tissues in different subjects. Some individuals are immune, others predisposed to benign, and still others to malignant, growths. Cancers produced by tar differ from those made with grafts. It may be that the benign tumors represent a stage toward malignancy. There are various forms, ranging from horny growth without infiltration or invasion by cancerous cells to ulceration with epitheliomatous structure. Two points of rather less importance are the frequency of multiple tumors and the predominantly carcinomatous nature of multiple tumors. Tumors arising from a single focus are more often benign. Moreover, the structure of the various tumors produced by tar has always been epithelial.

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**The Artificial Production of Metastasizing Mouse Carcinomas with the Constituents of Tar. Clinical and Histologic Investigations.**

*W. Dreifuss, Arch. f. Dermat. u. Syph., Berlin, 140: 6, April 29, 1922.*

Mice, rabbits and guinea-pigs were used as experimental animals and they were painted with tar every second to third day.

The first occurrence is a total loss of hair following a desquamation of the skin. This condition remains unchanged up to the appearance of the initial ulcerating and productive efflorescences, which usually occurs 3 months after the first painting. Either the most minute flat erosions or polygonal or round warts up to the size of a pinhead develop. Both of these initial efflorescences may disappear or develop into tumors. The tumors grow horizontally or vertically and the primary efflorescences increase in size with the formation of a tumor-like marginal wall. The flat erosions may undergo a change into tumor-like formations and the primary verrucous forms may become flat formations as the result of ulceration. The originally flat little tumors acquire a delicate papillary and distinctly hyperkeratotic surface. The edge, which must be considered as the true productive zone of the tumor, is usually represented by a hard wall, which is smooth and covered by intact epidermis.

It is sharply circumscribed and of a pale, gray-red color. Other tumors retain their flat form for a very long time, even up to the end. Spontaneous death occurs in about 5 or 6 months, except in animals which die from intercurrent disease.

The occurrence of true metastases is by far the most important finding in necropsies, being found in lymph nodes and particularly abundantly in the lungs. The primary changes and those determining the further development and the final result are found in the ectodermal portion of the skin. The hypertrophy affects all the layers of the skin. During the stage of tumor formation, the thickened epidermis begins to invade the deeper structures in smaller and broader ridges and sprouts, and a loose, vascular connective tissue, moderately rich in cells, inserts itself between the epithelia in narrow papillas. It is a noteworthy fact that even in this early stage the tendency to hornification is observable. The initial tumor grows in all directions. The epithelial sprouts proliferate energetically laterally and toward the deeper structures, undergo division and send branches in all directions. The absence of the normal inhibition and the malignancy of the growth in the true sense are made evident particularly in the beginning of the separation of individual epithelial strands from the original source and their independent proliferation in the deeper layers. Hand in hand with this infiltrative growth there goes also a change in the growing cell: sections can be seen, in which the nuclei show varying sizes, but always full of chromatin and with distinct structure; other portions show large pale nuclei, with exceptionally distinct framework, and nucleoli.

The polymorphism of individual tumors is not observed in by far the greatest number of metastases: in many places, even in the youngest proliferating parts, the structure is the same and the character of the normal epidermal cells is maintained to a high degree. One or more concentrically-layered horny pearls are frequently found within a cancerous strand, often surrounded by flat cells containing keratohyalin, especially in the metastases. Or there may be isolated or a few neighboring epithelial cells, whose protoplasm has become homogeneous and shows in a more or less marked manner the tinctorial properties of keratin. The abnormal character of the process of hornification is also evident from the fact that it may occur spontaneously, without the intermediation of the stage of keratohyalin, so that the horny pearl is directly surrounded by prickly cells. As a result of the growth of the tumor toward the free surface, cells and papillas frequently attain a considerable length and varying calibers. Destruction of the tumor tissue often occurs in the oldest and central portions; in these locations, large collections of leukocytes are usually found and a direct suppurative destruction of the tissue may occur.

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**Study of the Structure of Gall-Stones.**

*B. Naunyn, Arch. f. exper. Path. u. Pharmacol., Leipsic, 93:115, May 2, 1922.*

Very fine sections were made and fixed in isinglass or syndeticon. An enlargement of 30:1 to 70:1 was sufficient for examination of the specimens. In gall-stones which lie free in the gall-bladder, as contrasted

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with large solitary ones that are incarcerated in the bile ducts, a nucleus, a body and a shell can be distinguished. The body is either homogeneous and yellow to brown in color or consists of densely compressed spheruliths. The body is the chief constituent of the whole stones; both nucleus and shell may be lacking. The shell consists of several, never more than 10, layers which are formed by the adhesion of magma or the adsorption of cholesterin. There are currents of diffusion in the bile distinguishable by Liesegang's rings of precipitation. Their convexity indicates the direction of the current. Ordinarily the diffusion current passes outward. For the formation of gall-stones a diffusion current inward is indispensable, and Liesegang's rings are also found with the convexity inward. The carrier of colloid characteristics is chiefly the cholesterin.

The young stones, particularly the nucleus but also the magma, consists of bilirubin calcium and cholesterin, in addition to biliary acids, mucus and proteins. In time the bilirubin calcium is displaced by cholesterin that comes from the bile and the surrounding mucous membrane. The most important part of the building up of the stone is the body of the stone. The nucleus is never built up. If there is a central crystalline cholesterin structure it is a false nucleus, because it cannot have been the center around which the stone was built. In the body the building up of the stone takes place as a result of the dissolving of bilirubin calcium through the alkalinity of the diffusion current of the cholesterin. These processes are recognizable in the double rhythm of Liesegang's rings where among the concentric segments some are more strongly developed than others.

The spheruliths consist of bilirubin calcium and cholesterin and often undergo cholesterinization. Some of them are very clear and in that case show very beautiful Liesegang's lines. In addition to the precipitated segmental systems there are also marginal lines which encircle all the spheruliths. Often the whole body of the gall-stone consists of closely compressed spheruliths. Besides the 2 places named above in which Liesegang's lines appear, the false nucleus and the spheruliths, they appear often as free structures in stones soft as pulp, as fan-shaped segment systems. They must not be confused with the structures which develop when masses of cholesterin break through older layers of the shell. The remnants of the shell layers then have a slight resemblance to Liesegang's lines. The shell of the stone consists of 4 to 10 layers of a thickness of not more than 1 mm. which are formed by the deposition of cholesterin and bile. In the older deposited layers the cholesterin flocculates out and immediately undergoes surface action so that new layers are formed. These layers are marked off from one another by sharp lines which never show precipitations; the individual layers generally surround only a part of the stone.

In angular stones caused by mutual pressure, between the dark colored cholesterin layers there are deposits of bilirubin calcium. The mechanism is as follows: the stones are injured by pressure, and from the bile which enters at these points of injury bilirubin is absorbed and deposited between the formed layers. The deposited layers must not be confused with the internal lamellation of the body of the stone. The individual lamellas are very thin, about 0.03 mm. and often very beautifully colored. They may originate like Liesegang's rings by the forma-

tion of a precipitate in colloid media, but also by internal pressure in the stone itself. This pressure arises from the crystallizing out of cholesterin and the taking up of water of crystallization as well as by the deposition of cholesterin by adsorption. In the stratified shells of older stones there are often cones 0.02 mm. thick which consist of cholesterin in which a fine thread of bilirubin is barely distinguishable. These cones are connected with the masses of cholesterin in the body of the stone and grow into the shell or else are connected with a large external mass of cholesterin and grow into the shell. The internal cavity which develops on the first consolidation of the pulp-like mass, may be filled with fluid or cholesterin and may cicatrize or, by swelling of the cholesterin, may rupture the stone.

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**SECTION 1. ANATOMY, PHYSIOLOGY AND  
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**1a. ANATOMY AND PHYSIOLOGY**

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**Researches on the Structure of Striated Muscles.**

*H. Marcus, Anat. Anz., Jena, 55:475, July 10, 1922.*

The author's previous researches showed that the myofibril is not a solid homogeneous structure but a tube with fairly solid sheath and fairly fluid content. Accordingly the old hypothesis of a polyhedron with a transverse disk and telephragmas, with isotropic and anisotropic substance, should be abandoned, or other points, such as transverse striation, disk disintegration, etc., brought into harmony with the new conception. The author allowed sodium chlorid solutions in various concentration to act for different periods on the wing muscles of *Bombus* and determined the muscle weight and volume, the former by weighing (several animals together) before and after the experiment, the latter by microscopic measurement of longitudinal and cross sections after fixation and celloidin imbedding. Longitudinal sections always showed a central lumen bounded by darker margins, cross sections a darker ring around a brighter center. After disk degeneration from intumescence and subsequent evaporation, the disks corresponded to the Z, or rather to the C stripes, and showed distinctly a denser and darker margin. However, it was never possible to find an entirely dark disk corresponding to a transverse disk. The Z stripes are therefore Z rings; they are interconnected by radial cords of denser protoplasm. The myofibril is therefore surrounded by a sheath which is reinforced at certain intervals by the Z rings to which transverse supports are attached for connecting the individual fibrils into fasciculi. The sheath of the myofibril is a lattice work of solid elastic fibers between which a separating (semipermeable) liquid layer is spread, because by intumescence as well as by contraction distinct longitudinal striation can be produced in every myofibril. These fibrils are merely embedded in the sheath, as cross sections of intumescent fibers show a granulated ring as a border in place of a uniform dark ring. The most noteworthy effect of the action of sodium chlorid solutions of different concentration was that strong hypotonic solutions unexpectedly caused diminution of the fibrillar cross section (like in hypertonic solution); but in some cases it was noticed that cross sections of different size occur in the same preparation. The explanation for this is afforded by longitudinal sections or teased preparations in hypotonic solutions. Fibrils are found of thicker and thinner sections following upon each other in regular order like a rosary, which are related to the transverse striations. At the point of greatest width (about 3 microns) the fiber is darkest (C stripes) but in the optical section, as stated, the bright central lumen is seen. The rosary fibril (comparatively rare) is to be regarded as a transitional stage which is apparently capable of developing in two directions. An attempt was made at a comparison between increase of the muscle weight and increased volume of the fibril. It appears that in the intumescence of the muscle, water is first taken up uniformly into the fibril and the sarcoplasm, but with

increase of the intumescent process the fibrils again assume a smaller diameter, which signifies escape of substances through the lipoid sheath that has been rendered permeable. The rosary formation indicates that the region of the contractional stripe (of the transverse disk) is more resistant and less elastic after expansion in hypotonic solution and subsequent drying than the remaining part of the fibril and that the surface of the fibril sheath is therefore not uniform. Summarizing, two different substances are therefore to be assumed in the surface of the myofibril which alternate with each other at regular intervals, the main mass consisting of a lipoid body and the other, a comparatively narrow portion, of substance permeable to water.

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**On the Nature of Mitochondria. III. The Demonstration of Mitochondria by Bacteriologic Methods. IV. A Comparative Study of the Morphogenesis of Root-Nodule Bacteria and Chloroplasts.**

*Ivan E. Wallin, Am. J. Anat., 30:451, July 15, 1922.*

In Part III of Wallin's work the tissues used included lymph-nodes, liver, pancreas, kidney, salivary glands, thymus and other tissues. Immediately after removal from the previously killed animal, smears of the organs and tissues were made on microscopic slides and permitted to dry in the air without any other fixation. A large number of bacterial staining methods were later applied to the smear preparations, but the majority stained the entire smear so the mitochondria could not be distinguished. However, Wallin found that staining with saturated aqueous solutions of pyronin and methyl-green gave a sharp differentiation, and he has included in the article several camera lucida drawings of various tissues stained with this Pappenheim's pyronin methyl-green.

Part IV records author's microscopic study of a section of a root-nodule of the white clover which revealed the *Bacillus radiculicola*, a minute organism that may be found as a free-living bacterium in the soil. Under favorable conditions, it may enter the root hairs of Leguminosæ and exist in partial symbiosis. The host plant responds to the infection with a production of nodule cells. The invading organism comes to lodge in the cytoplasm of the root-nodule cells. In a mature root-nodule these forms, apparently, represent 3 stages in the morphogenesis of the bacillus after it acquires the symbiotic relationship. The morphogenesis of *B. radiculicola* from the juvenile to the senile forms is strikingly suggestive of the morphogenesis of chloroplasts.

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**Changes in the Vaginal Epithelium of the Guinea-Pig During the Oestrous Cycle.**

*Raymond M. Selle, Am. J. Anat., 30:429, July 15, 1922.*

For these observations common white, brown, and mixed-colored virgin female guinea-pigs were used. The determination of the state of progress of the oestrous cycle was based on a knowledge of the character of the contents of the vagina. A syringe method of sampling the vaginal contents was devised. A syringe of special structure and

containing about 1 c.c. of warm, normal, salt solution is introduced into the vagina to a depth of 25-40 mm. By forcing the contents of the syringe into the vagina once or twice, it is possible to get a characteristic sample of the cells in the lumen. In order to study the cycle, samples were taken at 8 a.m., 12 m., 4 p.m., and 8 p.m., and the results recorded. Animals were then killed during each stage as revealed by the character of the smears. Then the vagina was fixed in situ prior to its excision. A careful scrutiny of successive vaginal smears, of 20 guinea-pigs over a period of 7 months disclosed a succession of cell changes in the contents of the vagina. The following is a summary of the phenomena observed: (1) The length of the oestrous cycle of the guinea-pig is 15.87 days. (2) The cycle has 4 well-defined stages besides the interval. Stage 1: The epithelium is at its greatest height at the beginning of this stage, 10-12 cells. Cornification has been going on beneath the superficial layers. Vaginal smears contain large, vacuolated, granular, odd-shaped, epithelial cells. Stage 2: This is the stage of desquamation of the flattened, scalelike, nonnucleated cells—cornified cells. The inner cornified portion of the vaginal mucosa loosens and may be shed as a cast. Stage 3: Vaginal smears made during this stage contain round, nucleated, epithelial cells and some cornified cells which have remained from the preceding stage. Leukocytosis begins during this stage but leukocytes do not enter the lumen. Stage 4: During this stage leukocytes appear in the lumen of the vagina for the first time since the beginning of the cycle. Smears contain epithelial cells and leukocytes. During the interval vaginal smears contain leukocytes and mucus, but very few or no epithelial cells. The epithelium has become reduced to its lowest condition, 1-2 cells. The epithelium is rapidly regenerated at the end of the interval immediately preceding the next cycle.

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**Studies of Cell Division. I. The Effect of Dilute Sea-Water on the Fertilized Egg of *Echinarachnius Parma* during the Cleavage Cycle.**

*E. E. Just, Am. J. Physiol., 61:505, Aug. 1, 1922.*

When inseminated eggs of *Echinarachnius parma* are exposed to the action of dilute sea-water they take up water and swell; in sea-water of slight dilution they reach a point of equilibrium without disintegrating. They remain thus for a longer or shorter time which depends upon the degree of the dilution. If the dilution be great (30% of sea-water and less) the eggs swell and cytolysis. The rate of this cytolysis in a given dilution is most rapid in eggs that are exposed to the dilute sea-water just before cleavage. The rate of cytolysis of eggs while in dilute sea-water constitutes an excellent criterion for determining this period of susceptibility in the developing egg. The results are sharp and well defined. This is especially true if the cytolysis comes on rapidly, so the author used 100% tap-water in most of the observations. The period of susceptibility which the egg of *Echinarachnius parma* exhibits just before cleavage the author found undoubtedly comes on during the anaphase and telephase, while the egg is still spherical and before the hyalin plasma layer fully heaps up at the equator owing to its movement from the area over the spindle poles. This movement brings about a thinning of the hyalin plasma layer in the polar areas. The

susceptibility is due to a development of weakness in the cortex over the poles so that when the egg takes up water it rapidly bursts at these points.

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**Attempts at Imitating Cell Division and Karyokinetic Figures.**

*R. Beutner and M. Busse, Ztschr. f. d. ges. exper. Med., Berlin, 28:90, June 7, 1922.*

If one drop of India ink is placed in a potassium nitrate solution (up to 5%), there results at first an aster formation, then a reticular structure resembling a cell skein; finally the figure disintegrates and the whole is jumbled together into an undistinguishable mass. All potassium salt solutions gave such aster formations except potassium chlorid; the sodium salts were ineffective. The most pronounced effects were produced with potassium nitrate, potassium sulphate and potassium phosphate. Ammonium salts yielded no results; on the other hand, results obtained with calcium and rubidium salts were quite effective. The last attempts were made with salts of the heavy metals, especially copper salts. There was coagulation to a dilution up to 0.005%; below that there was aster formation.

All experiments seem to show that salts of high molecular weight yield more generally and readily the peculiar aster formation referred to than salts of low molecular weight. Hence the uselessness for this purpose of almost all sodium and ammonium salts, as well as of the chlorids, and the particular adaptability of potassium, rubidium and cesium salts. Furthermore, it is striking that organic substances, such as sugar, glycerin, or urea, yield very distinct aster formations. It would thus appear that, apart from the effects of coagulation, there comes into play a special property of the substance in solution.

Previous investigations have succeeded in bringing about some sort of differentiation of the dissolution products of colloidal substances, suggestive of biologic phenomena. But the fact that such decomposition of colloidal materials may be influenced by the chemical properties of the medium in its most special characteristics is entirely new, at least in the form in which it is here presented. In each of these experiments there appeared, in various colloidal systems and in the presence of definite substances in solution, regular figures suggestive of karyokinetic formations. It thus becomes possible to determine at will the appearance and characteristics of such figures. Further investigations along the lines indicated will no doubt unearth methods and procedures which will, in due time, give a solid, scientific basis to our present-day conceptions of elementary life phenomena such as cell division, mitosis, karyokinesis, etc.

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**Early Movements, Reflexes and Muscular Reactions of the Human Fetus, and Their Relation to the Fetal Nervous and Muscular Systems.**

*M. Minkowski, Schweiz. med. Wchnschr., Basel, 52:721, July 20, 1922.*

The author reports observations made in fetuses between the second and fifth months. These were kept at as constant a tem-

perature as possible in a vessel containing physiologic salt solution at 40° C. Most of the fetuses carried out motions of the head, trunk and extremities, which may best be described as choreato-athetotic, interrupted at times by markedly choreatic motions. In older fetuses there occurred expansion movements of the thorax, as well as opening and closing of the mouth.

Practically every section of the cutaneous surface served as a reflex-producing zone for very variable reactions, and these tend to extend over more or less the entire fetal organism. Together with "short" or crossed reflexes, there appeared "long" and "diagonal" reflexes, the latter of special biologic interest. Touching the lower lip or the tongue induced repeated opening and closing of the mouth. While the palpebral fissure had not yet developed, touching the eyelid resulted in a contraction of the orbicularis muscle. In one fetus measuring 6.5 cm., a patellar tendon reflex could be elicited, with a tendency to spread. Among the deep reflexes of the neck, those produced by altering the relative position of the head to the neck were tonic in character; they continued until the normal relation was established. When the position of the head in space was altered, the fetuses exhibited deep reflexes, undoubtedly belonging to the labyrinthine reflexes. (*To be continued*)

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**The Function of the Fetal Pancreas.**

*A. Giroud, J. de physiol. et de path. gén., Paris, 20:173, No. 2, 1922.*

Functional activity in the fetal pancreas is chiefly indicated by diminution of Claude Bernard's granules and the presence of secretory products in the lumens of the excretory ducts. The secretory products indicate secretion, but the latter may not be active. Comparison of the fetal with the adult cells shows that the size of the fetal granules increases much more slowly than that of the granules in the adult cells. Moreover, the adult cell refills with granules in a few hours, while many days are required to produce a similar effect in the embryo. The slowness of the production curve may be due to the factors of elaboration and collection of the granules.

Giroud has examined the pancreas of a young Didelphys, which probably secretes at an early period. Here variations of the size of the cells correspond to that of the mass of granules. Functional activity limits the number of the increasing secretion granules. This fact is probably true of other animals. The substance occupying the pancreatic acini is not due to crushing of the cells, but appears to be a true secretion. The fetal pancreatic cells are therefore probably not at complete rest. Secretion occurs in a minor degree, the stimulus being derived either from the maternal organism or from the fluids of the embryo.

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**Differential Susceptibility as a Basis for Modification and Control of Development in the Frog. II. Types of Modification Seen in Later Developmental Stages.**

*A. W. Bellamy, Am. J. Anat., 30:473, July 15, 1922.*

In a previous paper Bellamy presented data to show that the frog egg and embryo exhibit a differential susceptibility to such agents as

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KNC,  $\text{CH}_2\text{O}$ ,  $\text{KMnO}_4$ ,  $\text{LiCl}$ ,  $\text{HCl}$ ,  $\text{NaOH}$ , and  $\text{C}_2\text{H}_5\text{OH}$ . Those regions of the egg which differentiate earliest and in which growth is most rapid (apical and dorsal regions—in the early stages of development; in later stages any rapidly proliferating or physiologically active region) die soonest in concentrations of external agents that are lethal within a relatively short time; are most inhibited by somewhat lower concentrations, and acclimate or recover first in concentrations permitting acclimation and recovery. This present report is concerned with the modifications seen in the later stages of development—gastrulation to the time of hatching or a little later. The 4 types of modifications obtained are characterized as: differential inhibitions, differential accelerations, differential acclimations, and differential recoveries. The modifications produced are perfectly characteristic, not of a particular agent or condition, but of a particular concentration or intensity of action of that agent. The author found that differences in susceptibility parallel the axes of symmetry. Those regions which usually differentiate earliest and grow most rapidly are most distorted, the degree and direction of the distortion depending largely upon the severity of the treatment and physiologic condition of the organism.

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**The Fertilization Reaction in Echinarachnius Parma. V. The Existence in the Inseminated Egg of a Period of Special Susceptibility to Hypotonic Sea-Water.**

*E. E. Just, Am. J. Physiol., 61:516, Aug. 1, 1922.*

If eggs of *Echinarachnius parma* are placed under the microscope and inseminated, one may observe the rapid penetration of the sperm and with it the wave of negativity as evidenced by the behavior of supernumerary sperm around the egg. There then follows the period of about 15 seconds before membrane separation begins. The moment the membranes begin to lift the eggs are treated with tap-water. In 15-20 seconds after the tap-water is added the eggs burst. This cytolysis is violent, rapid and complete. But for the use of sea-water of graded hypotony it would be extremely difficult adequately to interpret this behavior. With the use, however, of sea-water ranging in dilutions from 95%-5%, the author has been able to reveal the whole period clearly. If the egg is treated with tap-water when the membrane is one-third or one-half off instead of at the moment of membrane separation, the result is the same—there is a complete cytolysis in some 15 seconds. If the egg is allowed to separate its membrane from its entire surface except the very last point opposite the site of sperm entry (from which the membrane lifts last) and is exposed at this instant, then cytolysis takes place as before.

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**An Anatomic and Embryologic Study of the Perineum.**

*Miley B. Wesson, California State J. Med., 20:269, Aug., 1922.*

From a study of serial sections of 31 human embryos Wesson concludes that Denonvillier's fascia is not formed by a fusion of the fetal pelvic peritoneal. The rectum, at the level of the prostate, is

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surrounded by a more or less definite cuff of connective tissue in which the lowest part of the peritoneal cavity dips. At no stage of the development is the peritoneum in contact with the prostate, it being always nearer to the rectum than to the prostate. The rectoprostatic space is filled at first with a syncytium or mass of embryonic connective tissue cells. Eventually differentiation occurs and there is a condensation of connective tissue anteriorly and posteriorly. The anterior layer covering the prostate is the thicker, and the elastic tissue fibrils predominate, thereby causing the shiny appearance characteristic of Denonvillier's fascia. A sheath of fascia surrounds the ejaculatory ducts and utricle as they pass through the prostate. The rectourethralis is a sheet of muscle arising from the external longitudinal layer of the rectum and ending in the raphe of the external vesical sphincter. In exposing the prostate by the perineal route, the rectourethralis muscle should be cut close to the central tendon, the incision being sufficiently deep to sever the posterior or rectal layer of Denonvillier's fascia, and the dissection continued anteriorly to the muscle, for if the posterior layer is followed, it leads directly into the rectum. If the incision is made anterior to the central tendon, the dissection leads first into the venous bulb, causing hemorrhage, and then through the external vesical sphincter; opening of the rectum is thus avoided, but there is a prolonged and often permanent loss of vesical sphincter control. Long Cowper's ducts ending near the meatus probably develop as periurethral ducts.

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#### **The Development of the Interstitial Gland in the Testicles and Ovary.**

*W. Lahm, Monatschr. f. Geburtsh. u. Gynäk., Berlin, 58:128, July, 1922.*

In both the ovaries and the testicles, cells are found which appear at various times in various numbers, in a form and arrangement which justify the assumption that they are concerned in the formation of interstitial glands (glands of internal secretion). Nothing definite is known as yet concerning the function of these interstitial glands, but they probably have some connection with fat metabolism. Practically all authorities agree that they have a trophic activity. Lahm designates them as the center of plastic stimulation; which indicates merely that this tissue has more than local significance. This assumption appears logical if one systematically studies the puberty glands in connection with certain physiologic and pathologic phenomena.

The investigations here discussed concerned embryos up to the second month, and traced the genesis of the cellular elements which, in the ovary, are doubtless derived from the connective tissue; in the testicles, in all probability, from the germinal epithelium. Lahm corroborates and explains the presence of the interstitial gland in man, which has been denied by some investigators. However, he disagrees with Steinach's interpretation of the puberty glands; and interprets Steinach's experiments, which advanced the problem of rejuvenation to such a remarkable degree, as indicating that the interstitial glands possess trophic properties, which, in atrophic conditions of the generative portion of the germinal gland, furnish the material for the res-

toration of the generative cells. In this manner the consequences of ligation of the vas deferens may be explained.

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**Changes in the Omentum of the Rabbit during Mild Irritations; with Special Reference to the Specificity of the Mesothelium.**

*R. S. Cunningham, Bull. Johns Hopkins Hosp., 33:257, July, 1922.*

There has been a good deal of uncertainty as to the specific identity and reaction of 3 classes of cells of mesoblastic origin which form a large part of the structure of the omentum, namely the serosal lining cells (mesothelium), the fibroblasts, and the clasmatocytes. Some workers think the serosal cells specifically distinct from the others, other workers consider that the mesothelium and fibroblasts are entirely interchangeable, and that the fibroblasts, for instance, can promptly replace damaged mesothelial cells. Cunningham has tested the question by causing mild irritation of the omental peritoneal surface in rabbits by laked homogeneous blood injected into the peritoneal cavity. Some of the rabbits were also given intravenous trypan blue. Preparations of the omentum were studied fresh, stained, and silvered. The result shows clearly that the serosal lining cells and the fibroblasts react differently as regards both their morphologic appearance and the distribution of their content of vital dye. The irritated serosal cells increase in thickness and become more compact than before irritation; the vital dye content is diffuse, but the dye never enters long processes which form as the cells retract and round up. On the other hand the fibroblasts become elaborately branched, and their processes are full of dye granules. The clasmatocytes round up somewhat when irritated, but retain their characteristic form. Cunningham concludes that not only are the mesothelial (serosal) cell and the fibroblast distinct, but they react differently to the stimulation of mild irritants.

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**The Survival of Cells after the Death of the Organism.**

*Warren H. Lewis and Charles C. McCoy, Bull. Johns Hopkins Hosp., 33:284, Aug., 1922.*

Modern cytologic methods have given us a criterion by which cells can be distinguished as dead or living, which depends upon the fact that almost all types of cells either contain a system of vacuoles having an affinity for neutral red and similar dyes, or they develop such vacuoles under deleterious conditions leading to slight injury. Dead cells no longer display these vacuoles, but stain diffusely with neutral red, and show a sharp and distinct nuclear membrane and a change in the texture of cytoplasm and nucleus. Lewis and McCoy have determined the length of time elapsing between the death of an animal (rat) and death of various of the body cells. The longest life of cells was found when whole organs were removed and kept at 37° F. Cells died sooner in small pieces at room temperature, and also when the whole carcass was kept at room temperature of 37° F.

The order of survival was: tissue macrophages, cartilage cells,

kidney tubule cells (all 240 hours) ; smooth muscle ; salivary, tracheal, tongue and bladder epithelium, capillary endothelium, lymphocytes, lung epithelium, leukocytes, Kupffer's cells, pancreas, erythrocytes, liver cells, mesenchyme, adrenal cells, intestinal epithelium, nerve cells. Brain cells survived less than one hour. Early death of intestinal epithelium was attributed to infection. Striated muscle does not develop the neutral red granules, and so could not be tested by this method. It is suggested that the long life of tissue macrophages, cartilage cells, and tongue and bladder epithelium is correlated with their anatomic position, relatively far from circulating blood. Kidney cells are functionally adapted to tolerate waste materials and therefore can well endure an accumulation of their own metabolic substances under the conditions of experiment.

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**Tissue Cultures.**

*Busse, Schweiz. med. Wchnschr, Basel, 52:701, July 13, 1922.*

If a fragment of rabbit tissue, e.g. of a cardiac valve or of the aorta, is placed in a drop of blood serum of the same animal under aseptic precautions, and the preparation, protected against drying, is placed in the incubator, small fibrils and "spears" can be seen to project from the edge of the tissue into the nutrient medium after an incubation period of 1-3 days. These fine processes are soon identified as protoplasmic outgrowths of spindle and stellate cells. If the culture finds suitable conditions and is not disturbed, these cells increase in size and form a dense network of anastomosing cells which surround the tissue transplant like a veil. When good care is taken of the culture (irrigation with sterile Ringer's solution and the addition of fresh plasma), the transplant may be kept for weeks and months, even years. Carrel and Ebeling have kept cultures alive for 7 years. In every transplant are found the highly differentiated spindle and stellate cells.

If the cultures are disturbed (usually by bacteria), round cells develop. When a bacterial colony develops in a medium at a distance from the tissue, these round cells can be seen to reach out toward and to collect in and around the colony. Since the formation of round cells takes place in pure cell cultures also, it is evident that they are derived from tissue cells and not from hypothetical leukocytes. Some of these round cells, from their nuclei, correspond to lymphocytes; others show the morphologic characteristics of eosinophil or neutrophil leukocytes. Until now these cells have not been proven to correspond to genuine leukocytes, as no oxydase reaction was obtained with them. Upon the addition of a weak dilution of Wilstaetter's peroxydase to a suspension of these cells the author obtained a positive oxydase reaction with these round cells after a few hours, both in fresh living cultures, and after formalin fixation. As a further result of the prolonged cultural experiments it was found that embryonic as well as adult tissues can be easily cultivated in heterologous protoplasm.

The author also reports 2 observations made by his collaborator, Vetter. The first deals with the use of vital stains for tissue cultures, especially neutral red, which differentiates well. The other relates to the phenomenon of motion in the cardiac valves of young and adult rabbits. Rhythmic contractions were observed radiating from the center

The law probably applies also to females. In certain experiments ovariectomy, in which a small mass of ovarian tissue was left, was not followed by the growth of spurs, the contrary resulting when ovariectomy is complete. A small fragment of ovarian tissue also served to arrest growth of a spur which had begun to develop. The spur growth was not slowed, but arrested abruptly. A certain minimum of hormonal tissue seems to be required for the production of morphologic changes. Sand finds the same true in rats.

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**Grown-Together Twins and the Last Illness of the Blazek Twins.**

*Benj. H. Breakstone, Illinois M. J., 42:123, Aug., 1922.*

Joined twins who have lived are rather few, but pathologic laboratories are full of these monstrosities. Teratology, or the science which treats of these anomalies and monstrosities, is not very well developed, and there is little published in the literature. Lack of development usually occurs in the median line, e. g. double harelip, cleft palate and spina bifida. Branchial cleft and cervical rib are rare exceptions; most of the double monstrosities occur on the side. The author describes the cases of several famous twins. He personally has seen several grown-together twins: the original Siamese twins who lived to be 64; a similar pair of twins shown with a circus who wished to be separated, and who were operated upon by Doyen in Paris—during the operation one of them died, and later the other succumbed; Lalloo, an East Indian grown-together twin from whose abdomen protruded the body of a female.

The twins which are now being shown with the Sells-Floto circus are at the present time 16 years of age, and have the most loose connection of any twins reported. They could easily be separated, as there are no organs in common, but their mother refused on account of the income derived. The same reason was given in the case of the Blazek twins. They were separate entities; pulse, respiration and temperatures were about the same, but the pulse varied with the excitement of one or the other. They had different likes and dislikes in the manner of food and drink, and different impressions of people and other subjects. They were two different individuals whose bodies united physically, and the only common thing was the rectum.

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**Two Rare Cases of Congenital Malformations.**

*Deeg, Beitr. z. klin. Chir., Tübingen, 126:429, 1922.*

The first case shows numerous malformations due to amniotic bands, from the superficial to the deep constriction furrow, harelip, syndactylism, spontaneous amputation and club-foot. Everywhere the effects of constricting bands can be seen. There is spontaneous amputation of the index and middle fingers of the left hand. In the presence of many other effects of amniotic bands, it is reasonable to attribute the syndactylism to the same cause by assuming that the traction of bands prevented the invagination of epithelium necessary to separate the



fingers. The lower left leg shows the most marked effect of the action of amniotic adhesions: there are circular furrows almost down to the bone, club-foot with numerous furrows on the toes, and phenomena of stasis and defective nutrition.

The second case is one of congenital partial gigantism in an otherwise normal child. There are no indications of hypophyseal disease. Another point of interest is the presence of a lipoma-like mass, which fits in with the opinion of several authors, that there are many points of resemblance between gigantism and tumor growth.

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**A Case of Persistence of the Ischiatic Artery on Both Sides.**

*Eduard Pernkopf, Anat. Anz., Jena, 55:536, July 25, 1922.*

Hochstetter has shown on mammalian embryos that the ischiatic artery temporarily fulfils the function of the main artery of the body. In birds and in reptiles this condition is permanent, while in adult man he regards the trunk of the inferior gluteal artery as the remnant of this primitive vessel. Occasionally the ischiatic artery persists in man as a large blood-vessel, continuing the hypogastric artery and passing into the popliteal artery, the femoral artery remaining rudimentary. In a female cadaver the author found the left femoral artery normal in course and diameter, ending in the popliteal artery. The otherwise normal hypogastric artery divided below the linea terminalis into two branches of approximately equal size. The dorsal branch showed normal relations as to position and ramification of the superior gluteal artery, while the ventral branch was evidently the continuation proper of the hypogastric artery, and from its further course might be designated as the ischiatic artery. Gradually decreasing in caliber, it descended in a caudal direction between the branches of the ischiatic nerve, and could be traced to the level of the slit in the adductor muscles, where it ended in a branch after giving off smaller twigs that entered the long head of the biceps femoris.

Similar conditions obtained in the extremity of the right side. This partial persistence of the original main arterial trunk is intermediate between the total persistence hitherto observed and normal development. Toldt reported a similar case in which in addition to the inferior gluteal artery penetrating the ischiatic nerve, there was a supernumerary inferior gluteal artery. In the opinion of the author, the latter represents the remnant of the ischiatic artery, just as does the persistent artery in his own case.

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**Supply of the Heart by Only One Coronary Artery.**

*Alfred Plaut, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:84, 1922.*

The absence of one coronary artery has apparently not been observed up to the present. According to Hyrtl a case could only be designated as such if the single coronary artery demonstrably supplies both sides of the heart, and not one in which an artery arising at another spot than at the ascending aorta replaces the apparently missing artery. In an anomaly described by Engelmann in 1898 no vessels arose in the

right sinus valsalva, but there was an atrophied coronary artery of abnormal origin at the ramus descendens of the left sinus; the blood supply of the right ventricle was effected for the most part by 2 strong branches of the left coronary artery, coursing through the anterior and posterior of the right ventricle, respectively. The case observed by the author resembles this case. In a 37 year old man the right coronary artery was missing at the customary point, while in the right sinus valsalva only a small dark brown spot could be seen, without the slightest trace of a lumen. The left coronary artery, arising at the normal point, supplied the whole heart; it wound around the whole heart in the sulcus coronarius and only 3 c.c. from the point at which the right coronary artery should arise it divided into small not easily dissectible branches. The ramification of the left coronary artery, which also supplied the right side of the heart, was essentially normal, the right one was absent except for the aforesaid small spot which may be regarded as a rudiment. Actual absence of a coronary artery has not been described so far even in cardiac malformations, except in Hyrtl's cases, in which the cardiac cavity, owing to a deficient septum, was single and the coronary arteries were therefore also represented by a single division. No case is known to comparative anatomy, not even in the elephant, as was once maintained. The occurrence of 2 coronary arteries is a phylogenetically late phenomenon and is probably a result of the complete separation of the two sides of the heart. Great variability still exists in Chelonia and Sauria, for in these there are at times one, and at others two, coronary arteries, and the points of origin also vary greatly.

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**Duplication of the Right Ventricle with Malformation of the Coronary Arteries.**

*Wilhelm Schöndube, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:195, 1922.*

In the heart of a 7 year old cow, slightly hypertrophied and conspicuous because of its peculiar shape, the right ventricle was enlarged at its lower right portion and formed a second apex at the level and to the right of the normal apex. On the anterior and posterior surface of the heart wall a large serpentine vessel coursed downward toward the apex. Examination of the heart cavities showed a second cavity distal to the right ventricle. This accessory ventricle reached downward to the level of the normal apex and communicated proximally, by means of a folded system having a communicating opening, with the normal ventricle. The abnormal apex had a very thin wall, at most 1.5 mm. thick. Into the accessory ventricle the aforesaid vessels had a common opening. These vessels proved to be the ramus descendens anterior and ramus circumflexus of the greatly hypertrophied and dilated left coronary artery. The supernumerary and middle (owing to the communicating opening), and also the normal right ventricle probably received arterial blood from both branches of the coronary artery, as it can hardly be assumed that the venous ventricular blood could have been forced during systole through these vessels into the aorta. An approximate arrest of the blood column in the supernumerary ventricle, on the assumption of nonparticipation of the latter in cardiac activity, is im-

probable, as no coagula were present. The abnormality must be explained as a partial double malformation. The original paired heart anlage (one anlage at each omphalomesenteric vein) became only imperfectly united, one half of the accessory ventricle becoming an appendage to the well-developed second half. Another possibility might be that the supernumerary ventricle originated from a congenital diverticulum of the heart through ectopia with a sternal fissure, but there was no evidence of the latter, whereas the system with the communicating opening also argues against this. Finally, an aneurysm of malformed coronary vessels might be involved. Histologic examination of these vessels showed a strong similarity between the point of transition of the coronary vessel walls into the wall of the supernumerary ventricle and an arterial vascular root of the heart. Between the ventricular musculature and the coronary vessels a purely connective tissue-like layer was interposed but by no means in a form characteristic for aneurysm. The author therefore concludes that the coronary vessels were normal when the double malformation was produced and that the supernumerary ventricle, as a small rudimentary cavity, had only a small connection with the ventricle; at the beginning of cardiac activity it also became active, owing to its muscular walls, and the small vascular connection of the initially empty supernumerary ventricle with the coronary vessels gradually expanded.

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**A Case of Fetal Umbilical Cord Hernia.**

*O. Ridder, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:305, 1922.*

Umbilical cord hernia belongs to the malformation sometimes seen in the newly born. Kermauner classifies umbilical cord hernias in respect to form and content as (1) simple umbilical cord hernia, (2) abdominal hernia, and (3) eventration. In most cases 3 different layers are found in the hernial sac. (1) The outer layer is composed of the abdominal skin, which continues at the base over the swelling and may form a wall 1-2 c.c. high. The continuation of this layer is the amnion, which may, however, be inserted directly into the abdominal skin. (2) Below this there lies a frequently more or less dense layer of Wharton's jelly. (3) Internally there is frequently a peritoneum, or rather a tissue corresponding to coelom epithelium, without blood-vessels. The contents consist principally of intestine, but the liver, omentum, kidneys, stomach, pancreas, spleen and all other abdominal organs may protrude. Cases have also been described in which the heart and lungs or uterus were found in the hernial sac. Between the individual organs and the hernial sac, as also between the organs themselves, adhesions are often found. In the occurrence of the malformations there is a preponderance of males, which has not been explained so far.

The author's case deals with a male fetus in the fourth fetal month with several malformations at the upper extremity and a peach-sized tumor of the anterior abdominal wall in which the umbilical cord terminates eccentrically. The upper part of the tumor contains the whole liver closely adherent to the thoracic wall, and the lower part a cartilaginous, freely movable loop of intestine as well as a portion of the

stomach and spleen and contracted omentum, cecum, and a part of the large intestine that resembles the other intestinal loops macroscopically. The testicles are in the abdominal cavity at the posterior surface of the anterior abdominal wall. Nothing noteworthy is found in the other organs. The malformation is explained by a developmental disturbance from unknown causes of the germinal layer with formation of an abdominal fissure and anlage of liver and intestine in the resulting hernial sac. The result of the examination of the present case may be summarized as follows: According to Kermauner's theory a developmental disturbance of the germinal layer is involved in medium and larger congenital abdominal or umbilical cord hernias, which prevents the growth of the abdominal muscular layer into the membrana reuniens inferior. This leads to fissure formation and to the anlage of the liver and intestine in the resultant hernial sac. It remains to be considered that no factors are found in the fetus or in its appendages to warrant the assumption of a mechanical origin. All the aforesaid points justify the assumption that a disturbance of development is involved, irrespective of whether the inciting factor is in the ovum itself or in an injury of the ovum during the earliest segmentation stages.

## GENERAL PHYSIOLOGY

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### **Bacteriologic Investigations on the Validity of the So-Called Arndt-Schulz Fundamental Biologic Law.**

*Süple, Münch. med. Wchnschr.*, 69:920, June 23, 1922.

According to Arndt's teaching, weak stimuli arouse the vital activity, medium strong stimuli promote it and the strongest inhibit it. His teachings are based on the Pflüger law of spasms. Schulz supports the view that the action of drugs, by and large, is analogous to the law of spasms of normal nerves. According to Arndt, the effect of the stimulus does not depend upon its absolute intensity, but also upon the irritability of the cell, or of the organism. For this reason, the identical stimulus may be weak for normal irritable cells and organisms, but strong for hypernormal, irritable individuals. The author wanted to determine whether it is possible to demonstrate an accelerating effect of graded amounts of bacterial poisons on bacteria in an unmistakable manner, in order to solve in this way the problem as to whether the accelerating effects of the smallest amounts of poison are uniform or applicable only to certain substances. In accordance with the results of his experiments, he found a number of bacterial poisons, which accelerate the bacterial growth in artificial media in certain amounts. This proof was unquestionably successful with the following bacterial poisons: chlorinated lime, arsenic trioxid, copper chlorid, silver nitrate, mercuric chlorid, mercuric iodid, chromic acid, formaldehyd, formic acid, acetic acid, citric acid, phenol, lysol, grotan, thymol, resorcin, benzoic acid, salicylic acid, malachite green, gentian violet, methyl violet, crystal violet, methyl orange and safranin. The author convinced himself that with a series of substances, certain larger doses inhibit the bacterial reproduction, whereas smaller doses show no effect whatever. The findings of Schulz can therefore not be confirmed in regard to all substances. If the so-called Arndt-Schulz law has no unlimited validity

in the series of bacterial poisons it cannot be said to be a universally valid law, to say nothing of a fundamental biologic law.

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**The Responses of Fundulus to White, Black and Darkness.**

*G. H. Parker and A. J. Lanchner, Am. J. Physiol., 61:548, Aug. 1, 1922.*

To ascertain how much the illumination of the environment influences the tint of Fundulus, the authors kept a number of killifish for several days in white dishes exposed to daylight until they became light colored and retained this tint persistently. Three large battery jars were filled with water and a few of these uniformly light fishes were placed in each jar. Then each one of these jars was put for 24 hours in one of the following boxes: The first box, or white box, was lined with dull white paper and one side was left open so that the interior could be illuminated by an incandescent electric lamp (Mazda, 100 W.). A second box, the black box, was like the first in all respects except that it was lined with dead black paper instead of white. The third box, the dark box, was arranged so that it could be closed and was made absolutely light-proof. The 3 boxes were set up in a large dark-room so that the surroundings would have no special influence. On examining the fishes after the tests it was found that those in the white box were light colored, those in the dark box were as light colored as the fishes in the white box and those in the black box were dark in tint. After a few seconds the fishes from the dark box grew dark reaching a maximum in about half a minute. They remained dark for about five minutes, after which they took on the light tint normal for their surroundings and remained indefinitely in this state. If the fishes were temporarily blinded before being put in the boxes they did not lose their original color.

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**Metric Researches on the Degree of Validity of Spectral Color Equations, Being at the Same Time a Contribution to the Experimental Criticism of the Three-Components Theory of the Color Sense.**

*H. Goldmann, Arch. f. d. ges. Physiol., Berlin, 194:490, May 17, 1922.*

The experiments were conducted with Hering's original spectral light-compounding apparatus whose construction is described in detail. The conclusions are: The optical equations obtained with this apparatus between a homogeneous spectral light and a mixture of 2 spectral lights embracing between them a primary colored light (primary yellow, primary green, primary blue in Hering's sense) were found by the author, acting as observer, to show an incomplete degree of validity. It is true the author is relatively blue-sighted, so that a certain hyposensitiveness to red must be attributed, not to physical, but to physiologic conditions; for example, the relation between the quotient of the proportional value of red to green of his eye and the same quotient of a normal eye is not constant.



The optical equations were found to be mere tone equations in which the bisegment produced by binary mixture remains less saturated. Herein, according to Hering, the visual perceptions are represented in a three-dimensional manifoldness whose variables are formed by color tone, saturation and nuance. It is clear that equations exist whose degree of validity is restricted to agreement in brightness and others whose degree of validity is restricted to color tone, i. e., equations having a complete degree of validity, of which only the second kind is involved here. A complete equation is attainable in these experiments only by admixture of white light to the homogeneous bisegment. On following these equations in extended experimental series by very exact measurement, the spectrum showed 3 very distinct aggregation maxima for the saturation difference and thereby 3 points distinguished by optimum color saturation, which agreed in one and the same experimental individual under otherwise equal time and other conditions, with that individual's 3 primary colored spectral lights. In the case of the author as well as in that of another normal-sighted, possibly yellow-sighted, individual, the position of the saturation maximum, and parallel thereto that of the primary colored portion in the green, showed a characteristic variation, the origin and significance of which are as yet unexplained. Corresponding to the 3 primary colored cardinal points, the tracing of the spectral colors in the color field, with respect to the limiting line of their color plane, shows 3 distinct angles between which relatively rectilinear stretches are seen. The form of the resulting color plane is found to be not a triangle, but a quadrilateral whose fourth side would be formed by the primary red not represented in the spectrum. Accordingly 4. paired, coupled receptors or elementary reagents can be deduced in the visual organ. The color system obeys Newton's rule; it is three-dimensional. What these 3 coördinates are is thus far uncertain. Their selection is left to theory. Therefore mere representability by 3 coördinates furnishes no manner of proof of any of the color theories, inasmuch as Young-Helmholtz's as well as E. Hering's satisfies the requirement of three-dimensionality. But only Hering's theory is able to conform to the determination of that coupling of each 2 of the 4 fundamental colors which expresses itself in the aforementioned quadrilateral form of the color plane.

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**Observations on the Melanophores of the Frog.**

*K. Uyeno, J. Physiol., London, 56:349, July 21, 1922.*

For investigating the effect of carbon dioxid and of oxygen on the cutaneous melanophores, the legs of a frog were cut off immediately after death, one being placed in 0.6% NaCl solution in an atmosphere of oxygen, the other in the same solution in an atmosphere of carbon dioxid, and from time to time the state of the melanophores in the webs was observed. The author found that oxygen accelerates the postmortem concentration of the pigment in the cutaneous melanophores of the frog, while carbonic acid acts in the reverse manner. The action of these two substances upon the deep-lying melanophores was not conspicuous, but the author believes that some effect in the same direction as in the case of skin melanophores exists.

## CIRCULATORY SYSTEM

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### **Estimation of Cardiac Volume in the Living Animal by Means of the Teleroentgenogram.**

*John H. Skavlem, Am. J. Physiol., 61:501, Aug. 1, 1922.*

This study comprises a comparison of the volume of the heart of the dog as computed from the x-ray silhouette in the living animal and as measured directly after death and removal from the body. The animal is placed in the ventral prone position with the chest resting immediately upon the x-ray plate holder. The distance from the front of the chest to the film is only the thickness of a thin aluminum plate and an intensifying screen. The distance from the target to the film is 1 m. By such a position a clear-cut shadow of the heart is obtained which can easily be traced on all its borders. The measurement of the silhouette area is accurately and easily made by a planimeter. The measurement, however, must be reduced for the error made by the divergence of the x-rays in their travel from the target to the film. This error is corrected by a simple mathematic procedure. The distance of the film from the target being 1 m., it follows that  $A:B=X:Y$ , where A indicates size of x-ray silhouette area, B actual heart area, X distance of film from target, and Y distance of heart outline from target. The author made the last measurement from the plane of greatest area of the heart as determined after the thorax was opened. The relation of the volume of the dog's heart to the area of the x-ray silhouette made in the frontal plane may be expressed by the formula  $0.44A\frac{1}{2}$ . Volume determinations so made are accurate to 10%.

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### **Voluntary Acceleration of the Heart.**

*N. B. Taylor and H. G. Cameron, Am. J. Physiol., 61:385, Aug. 1, 1922.*

A case of voluntary acceleration of the heart is herewith reported. The subject is a healthy male, 26 years old, and at the word of command is able to increase immediately the rate of the heart from 50 to 70%. The reaction time, that is, the time which elapses from the moment the word to accelerate is given by the observer to the first indication of increased rate, is very brief, being usually about the length of one normal beat. The rate does not attain its maximum speed at once but takes several seconds to do so. Upon the signal to stop the rate drops instantly to normal and remains so for 6-10 seconds. The rate subsequently drops below the normal and remains at about 60 per minute for 25 seconds or so and then gradually increases until the normal is regained. It was observed that dilatation of the pupils, vasoconstriction and elevation of the blood pressure were associated with the increased heart rate. Atropin administration depressed but did not abolish the power of voluntary acceleration. A marked glycosuria was observed after a series of acceleratory efforts on the part of the subject. The authors believe the cardiac acceleration is due in part to the withdrawal of vagal tone and in part to excitation of the accelerators, the

two influences being called into reciprocal action by the voluntary effort.

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**Reflex Excitation of the Cardiac Fibers of the Pneumogastric Nerve from Arnold's Nerve.**

*Ferd. Scheminzy, Arch. f. d. ges. Physiol., Berlin, 194:527, May 17, 1922.*

Although a reflex influence on cardiac activity by the pneumogastric proceeding from various nerves, particularly from the trigeminus (Aschner's bulb pressure experiment), has been described frequently, experiments on a like influence proceeding from the sensory branches of the pneumogastric itself have not been submitted as yet. To investigate this question Arnold's nerve was irritated mechanically, thermally and electrically in the external auditory meatus, the pulse curve being registered after Jaquet by a sphygmograph and the registration of unusually long curves insured by means of a special device. The experiments were carried out on 29 individuals. The carotid pulse was also recorded by means of a funnel and a Marey's tambour and the arm's plethysmogram obtained according to Lehmann.

In the majority of the healthy experimental persons a distinct chronotropic effect of excitation was demonstrable by the slowing of the pulse, but in some cases acceleration of the pulse took place regularly. The same result was, however, attainable by excitation from the pinna, that is, from a spinally innervated cutaneous region, without any difference in the cardiac effect, from excitation of the pneumogastric fibers or of the nervus auricularis magnus, being perceivable. The differences in respect to the chronotropic action may depend on the existence of either excitation or arrest of excitation in the pneumogastric, but a reflex influence on the sympathetic may also be involved. No differences were found between men and women.

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**A Statistical Study of the Pulse Rate and the Arterial Blood Pressures in Recumbency, Standing, and after a Standard Exercise.**

*Edward C. Schneider and Dorothy Truesdell, Am. J. Physiol., 61:429, Aug. 1, 1922.*

The authors studied the pulse rate and the 3 arterial pressures—systolic, diastolic and pulse pressures—under 4 conditions, viz. recumbency, standing, immediately, and 2 minutes, after a standard exercise. The usual procedure was to require the subject to recline for 5 minutes and then to count the pulse rate for 20 or 30 seconds, the count being continued until 2 consecutive intervals gave the same result. After this the arterial blood pressures were determined. The subject then stood at ease for 1 or 2 minutes to allow the pulse to assume a uniform rate. When 2 consecutive counts of the pulse rate were the same, this rate was recorded and the arterial pressures for the standing position were then determined. The subject next stepped on a chair about 18 inches high 5 times in 15 seconds. As soon as both feet were on the floor after taking the exercise the pulse rate was counted for 15 seconds, and after that

the arterial pressures were determined. Following this the subject stood at ease for the remainder of a 2 minute period, when the pulse rate and arterial pressures were again determined. The greater part of this investigation deals with 2000 aviators whose ages ranged between 18 and 42 years. In order to have a check on them, 200 additional unselected cases were even more carefully examined and compared with the large group; in addition, a study was made of 2 small groups of men who were judged to be physically fit. A study of the detailed tabulated and graphic data resulting from these experiments shows that in the unselected groups a reclining pulse rate of 74 and 75 rose to 92 and 90 on standing, to 102 after exercise, and after 2 minutes was slightly below the original standing rate in the majority of cases. In the selected groups of physically fit men a reclining pulse rate of 72 and 70 rose to 86 and 83 on standing and to 97 and 95 after exercise. Taking the reclining pulse rate as a basis, it was found that the reclining to standing pulse difference varied inversely with the reclining pulse rate, i. e. the higher the reclining pulse the less the increase and vice versa. In the large group of 2000 unselected cases, the mean reclining systolic pressure was 118 and the standing systolic 120, indicating an increase on standing. The systolic of a physically fit group rose from a reclining figure of 112 to 118, a greater increase than in either of the other groups. Regarding the diastolic pressure, a reclining diastolic of 72 rising to 80 on standing, falling 2 mm. after exercise and returning to the original standing level in 2 minutes, was found to be the average picture. A reclining pulse pressure of 47, falling to 42 on standing, increasing to 50 after exercise and falling 2 mm. below the original standing after 2 minutes represents the mean. The higher the reclining pulse pressure the greater was the tendency to fall on standing, while a low pulse pressure might remain the same or even rise.

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**On the Coronary Circulation in the Heart-Lung Preparation.**

*Tomoichi Nakagawa, J. Physiol., London, 56:340, July 21, 1922.*

Most of the author's experiments were performed on medium sized dogs which were anesthetized with morphia and C.-E. mixture and then given an intravenous dose of chloralose, 1 gm. per kilogram. A heart-lung preparation was made as described by Knowlton and Starling. The arterial pressure was measured by a mercurial manometer which was connected with the side branch from the arterial cannula. From the venous end of the apparatus the blood was allowed to flow into a graduated cylinder, and the time taken to collect 50 c.c. determined by means of a stop-watch. This amount was the arterial output, i. e. the output of the heart minus the blood flowing through the coronary arteries. The coronary outflow was measured by collecting the blood through a Morawitz cannula introduced into the coronary sinus, and the time taken to collect 10 c.c. was noted. The blood flowing through the cannula was returned to the venous reservoir every few minutes, but it was necessary to circulate fresh amounts of blood to

remove the effect of vasodilator metabolites. In each experiment it was found necessary to use blood from one or two other dogs. The blood was defibrinated. The author first investigated the influence of the pericardial fluid on the coronary circulation, employing de Barenne's method of leading the blood from the venous reservoir directly into the pulmonary artery. The effects of pericardial effusion were imitated by allowing liquid paraffin at about 30° C. to flow into the pericardial sac. The tabulated results show that there may be a considerable amount of fluid in the pericardium, sufficient to diminish materially the filling of the heart, without altering the flow through the coronary vessels. The author also determined the effect of varying the venous inflow, and thereby the filling of the heart, on the output from the coronary sinus. The effect of the venous inflow was found to be very slight. To determine the influence of temperature on the coronary circulation, the coronary blood collected was not returned to the reservoir but was kept in the thermostat so that any effect of metabolites was removed. The tabulated results show that when the temperature is lowered, the number of the heart beats is decreased, while the coronary flow is increased at a certain lower temperature. In most of the author's cases the optimum temperature was 29°-31° C. In studying the influence of the rate of the heart beat on the coronary circulation, the author found that the coronary outflow is not influenced by acceleration or by slowing of the heart.

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**On the Relation of Blood Volume to Tissue Nutrition. I. The Effects of Hemorrhage on the Circulatory and Respiratory Response to Changes in the Percentage of Oxygen and Carbon Dioxid in the Respired Air.**

*Robert Gesell, Edward Blair and Robert T. Trotter, Am. J. Physiol., 61:399, Aug. 1, 1922.*

The purpose of this series of investigations was to determine by the employment of various methods the relation of blood volume to the nutrition of tissues. The series of experiments described in this paper involve the circulatory and respiratory response of the dog to a gradual reduction in the percentage of oxygen in the respired air when the carbon dioxid is absorbed and when it is allowed to accumulate. Un-anesthetized dogs were connected by means of a soft rubber mask to a Henderson rebreathing apparatus arranged to record accurately the total ventilation and to absorb or not to absorb the carbon dioxid eliminated in the expired air as the oxygen in the tank was consumed. The animal was held in a comfortable position throughout the experiment. One liter of room air was allowed per kilogram of body weight. With this allotment of air the experiments lasted 25-30 minutes, during which time respiration and time in seconds were continuously recorded on smoked paper. In addition the pulse rate was determined at intervals of 1-2 minutes, and air samples for analysis were drawn at approximately 7 minute intervals. Pulse rate, respiratory rate, total ventilation in cubic centimeters per kilogram of body weight per minute, and oxygen ventilation in 0.1 c.c. per kilogram of body weight per minute were

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plotted on the ordinates against the percentage of oxygen in the respired air on the abscissae. By plotting the time on the ordinates against the percentage of oxygen on the abscissae an approximately straight line (oxygen line) was obtained. The points on the smoked record at which the respiratory response and the heart rate were determined were set off on the oxygen line, giving the value of the percentage of oxygen on the abscissae. This permitted the plotting of the response at any number of points against the percentage of oxygen in the respired air.

The animals were encouraged to continue the experiment to the point of maximum endurance, which point the authors termed the breaking point. Some of the experiments were performed before hemorrhage and others after blood had been drawn from the external jugular vein by means of a large syringe. In summarizing the effects of hemorrhage the authors remark that while the elevated pulse rate noted at the beginning of all experiments following hemorrhage indicates a disturbance in circulation, analysis of the circulatory and respiratory response at the close of experiments when the organism is taxed to its utmost showed no striking difference in two of the dogs as a result of hemorrhage. In addition an analysis of the graphic results showed in one dog a postponement of the breaking point resulting from hemorrhage.

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**On the Relation of Blood Volume to Tissue Nutrition. II. The Effects of Graded Hemorrhage on the Volume Flow of Blood through the Striated Muscle of the Dog.**

*Robert Gesell and C. A. Moyle, Am. J. Physiol., 61:412, Aug. 1, 1922.*

In the authors' experiments the volume flow of blood through the leg muscles of the morphinized dog was measured. To record the blood flow a cannula was inserted in the femoral vein, this being ligated a short distance below, allowing blood to enter it from any single lateral branch carrying a flow not too great for registration with the drop method. Mean blood pressure and pulse rate were recorded with a mercury manometer connected with the left carotoid artery. Blood was drawn either from this artery or the femoral artery at intervals of approximately 10 minutes. The blood volume was increased by the injection of a 6% gum arabic suspension in a 0.9% sodium chlorid solution. The tabulated results show that hemorrhage, with one exception, invariably produced a decrease in the volume flow of blood. On the whole the hemorrhages occurring later in the experiments had a greater effect upon the volume flow of blood and mean blood pressure than the initial hemorrhages, invariably decreasing the volume flow of blood in disproportion to the decrease in blood volume. The effects of initial hemorrhage on volume flow of blood were found to be more variable, ranging from a decrease in volume flow of blood less than or equal to the reduction in blood volume to one far in excess of the reduction in blood volume. In experiments in which the injection of gum saline solution proved nontoxic, injection increased the volume flow of blood out of proportion to the increased blood volume.

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**On the Relation of Blood Volume to Tissue Nutrition. III. The Effects of Hemorrhage and Subsequent Intravenous Injection of Gum-Saline Solution on the Response of Striated Muscle to Rapid Stimulation, with Supplementary Data on the Effects of Hemorrhage and Infusion on Salivary Secretion Elicited by Intravenous Injection of Pilocarpin.**

*Robert Gesell and C. A. Moyle, Am. J. Physiol., 61:420, Aug. 1, 1922.*

The object of the authors' experiments was to determine whether or not changes in nutrient flow elicited by hemorrhage and subsequent infusion of gum-saline solution affected the response of the muscle to rhythmic stimulation. Contractions of the sartorius muscle of the anesthetized dog were studied. The insertion on the bone was severed with minimum interference with the circulation of the muscle and the tendon attached by a system of pulleys to a muscle lever the tension on which could be adjusted. Through specially constructed electrodes the muscle received rhythmic break shocks from an inductorium. Mean blood pressure was recorded with the mercury manometer. Time was recorded in seconds. Two procedures were followed in the study of the effects of hemorrhage and of infusion of gum-saline solution on muscular contraction. In one the muscle was stimulated equal periods of time at a rate producing, or not quite producing, complete tetanus, these periods being interrupted, with some few exceptions, with equal periods of rest. Having obtained at least two myograms similar in contour and suitable for controls, two more sets of contractions were obtained by the authors by similar stimulation after similar periods of rest immediately after hemorrhage, these records in turn being followed by myograms elicited after intravenous injection of gum-saline solution. In the second procedure long continued uninterrupted stimulation at a constant but slower rate was employed. The rate was such that tetanic contraction was never approached. If marked fatigue occurred the rate of stimulation was adjusted so that a fairly constant fatigue level was ultimately established. After having obtained such a fatigue level, the animal was bled and later injected without cessation of stimulation. In the 2 procedures the height and amplitude of contraction were used as indices to the effects of changes in blood volume resulting from hemorrhage and infusion. A study of the tabulated and graphic data resulting from these experiments shows that in general hemorrhage decreased the ability of the muscle to respond to stimulation and that injection of gum-saline solution improved the response. The authors also observed that hemorrhage and injection had corresponding inhibitory and accelerating effects upon salivary secretion elicited by the intravenous injection of pilocarpin. Injection of gum-saline solution in amount considerably greater than the hemorrhage increased the volume flow of blood and the flow of saliva considerably above the prehemorrhage flows. The authors believe the experiments indicate that augmented metabolism is closely dependent upon nutrient flow; that the decreased response of muscle after hemorrhage is due in large part to the decrease in flow of nutrient material to the tissues, and a decrease in flow of constituents which neutralize and carry away the metabolites.

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**Studies on the Physiology of Capillaries. V. The Reaction of the Human Skin Capillaries to Drugs and Other Stimuli.**

*E. B. Carrier, Am. J. Physiol., 61:528, Aug. 1, 1922.*

This paper concerns itself with the morphology of the capillaries in health and their reaction to certain drugs and other stimuli. The source of illumination was an arc lamp. The light was focused with a lens. The microscopes were a Greenough binocular, with oculars 1 and 3, objective 25 mm. and a magnification of 38 and 61 times, also a Zeiss microscope, with oculars 2 and 4 and objective AA magnifying 50 and 90 times. The places observed were the base of the nails on the third, fourth and fifth fingers, the back of the hand and sometimes the wrist and forearm. The effect of temperature and mechanic stimulation was observed, as was the effect of various drugs. The author found that on the back of the hand normally only a part of the capillaries in a given field is open at one time, but all may be easily stimulated to open by light pressure. Cold produces a contraction of arterioles with a slowing in the blood stream and contraction of the capillary wall. When the cold becomes extreme, the capillaries are paralyzed, open up and fill ultimately with venous blood. Stroking an area of skin with a blunt point opens all the underlying vessels. This initial flush is followed by the usual dermatographic reactions.

The effect of the following drugs was tried by using a fine capillary glass needle which could be run into the skin and brought to the side of a single capillary loop: Adrenalin, 1:1000 up to 1:100,000, produced contraction of both capillaries and arterioles. Histamin, 1:1000 up to 1:10,000, at the end of the nail produced dilatation of the capillaries with hastening of the blood stream; Pituitrin up to 1:100 produced contraction of the capillaries. Acetylcholin, 1:5000 and 1:10,000, dilated both capillaries and arterioles. Amyl nitrite, undiluted, dilated the capillaries slightly and increased the rapidity of the stream. When inhaled, all the capillaries were open with a very rapid flow. Urethan, 25%, dilated both arterioles and capillaries. All the observations agree with the view that the diameter of the capillaries is not necessarily dependent on the pressure in the arterioles, but rather on their own tone and state of contraction. They normally contract or relax independently of the pressure behind them, but in response to local or general stimuli.

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**Structure and Physiology of Nail-Bed Capillaries in Normal Individuals.**

*Walter Dieter and Chou Sung-Sheng, Ztschr, f. d. ges. exper. Med., Berlin, 28:234, June 7, 1922.*

In 500 normal individuals between the ages of 20 and 30, the capillaries on the nail-beds of all 10 fingers were subjected to examination, on strips of tissue 3 mm. in length and 0.15 mm. wide, and determinations made of the caliber, length, number in any one such strip, the form, and circulatory connections. The diameter of arterial capillaries varied between 0.01 and 0.03 mm., that of venous capillaries averaging

0.05 mm. Communicating vessels were often absent. There were apparently no great differences between arterial and venous capillary trunks. The length of capillary vessels seemed to depend (1) on the total length of the strip of tissue examined and (2) on the visibility of capillaries, which latter, in its turn, is determined by (a) consistency of the epidermis, (b) moisture content of the tissues, (c) situation of capillaries with respect to general circulation, and (d) intensity of illumination. The average figures calculated from a large number of observations were 160 to 400 in 60% of specimens examined, and 400 to 500 in 30% of specimens. There were 30 to 40 networks of capillaries to each of the cutaneous strips above referred to. The direction and rate of the blood current were anything but uniform in the various capillary plexuses and vessels, varying often within the same plexus.

Warmth causes dilatation of capillaries and acceleration of the blood flow; cold results in constriction and stasis; but as all such agents are difficult to restrict in their local action exclusively to the capillaries, results may be misleading. It was thus impossible to determine accurately the exact conditions making for active constriction of the capillaries in the strictest sense. Variations in the size of the lumen of capillaries could be brought about by mechanical, chemical or thermic stimuli, rendering possible in this manner a direct control of the blood flow within the small vessels. Variations in rate of blood flow, while mainly determined by changes in the arteries and arterioles, could in part at least be brought about by independent variations in the lumen of capillaries.

## DIGESTIVE SYSTEM

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**Studies on the Physiology of the Liver. II. The Effect of the Removal of the Liver on the Blood Sugar Level.**

*Frank C. Mann and Thomas Byrd Magath, Arch. Int. Med., 30:73, July, 1922.*

The amount of blood sugar exactly paralleled the clinical condition. The blood sugar concentration immediately after hepatectomy was the same or less than that preceding operation, and very rarely 0.01% higher. It decreased during the period immediately following the operation when the animal appeared normal. In most of the dogs the level of blood sugar at which the first symptoms developed was 0.05%. In some instances the first symptoms were noted when the blood sugar was 0.06%, and often when it was 0.04%. The blood sugar decreased quite rapidly after the onset of convulsions, and at the time of death was usually not in excess of 0.03%. This direct relationship of blood sugar and the development of symptoms and death were so constant that the blood sugar could be estimated correctly after an examination of the animal's clinical condition when it showed symptoms. In one carefully performed experiment a specimen of muscle was excised at the same time the liver was removed. When the animal became moribund, another specimen of muscle was taken. An estimation of the glycogen content of these 2 specimens of muscle revealed that the glycogen had decreased about 50%. After extirpation of the liver in the

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goose, the blood sugar does not fall. In all specimens of frog's blood examined after removal of the liver and at time of death, the blood sugar was too low to estimate. In the fishes studied (garpike and dog-fish), removal of the liver caused a marked decrease. The effect on the turtle, which normally has a relatively high blood sugar, was the same as on the fishes.

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**Studies on the Physiology of the Liver. III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver.**

*Frank C. Mann and Thomas Byrd Magath, Arch. Int. Med., 30:171, Aug., 1922.*

An animal dying from the removal of the liver, comatose and perfectly flaccid, apparently unable to contract any muscle except the diaphragm, was restored immediately to a seemingly normal condition by the injection of from 0.25-0.5 gm. glucose for each kilogram of body weight. Such an animal may stand 30 seconds after the injection of glucose, walk, respond to call, wag his tail, drink water, in less than 1 minute from the time it had been perfectly flaccid. Immediately after the injection of glucose, the blood sugar reached a very high level. At first it decreased quickly, then fell more slowly. As the level again became low the typical symptoms reappeared. The time that this occurred after injection depended upon the amount of glucose injected, whether the animal was active or quiet, and whether or not it was kept warm. Restoration of the animal from the comatose condition could be repeated many times. In each instance the clinical condition exactly coincided with the blood sugar level. Finally, however, usually after many restorations, it was noted that the same amount of glucose did not maintain the animal in a normal condition for so long a time, and the characteristic symptoms developed at a higher blood sugar level.

At this stage of the experiment another condition developed and other symptoms appeared. These differed in different animals. Some animals suddenly became comatose and remained so for a variable period, usually not more than an hour, and died suddenly and quietly. In others the symptoms were similar to those following excessive feeding of meat to animals with Eck's fistula. The animal was at first quite restless, ataxia then appeared, and sight and hearing were lost; coma developed and death was sudden and quiet. Anuria usually accompanied this second moribund condition. The blood sugar level might be high and the injection of glucose was without beneficial effect. The cause of this second condition has not been determined, but it seems to be dependent on some change in metabolism other than carbohydrate. In some experiments, before the blood sugar had decreased to a lower level and before symptoms had occurred, glucose was injected slowly at a fairly uniform rate with a continuous injection machine. In this manner the blood sugar level was kept normal or slightly above normal. The first group of symptoms never developed in these animals, but after 18-24 hours the second group developed and the animals died.



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**The Spleen and Digestion. III. The Spleen in Inanition; the Effect of the Removal of the External Secretion of the Pancreas on the Spleen.**

*William DeP. Inlow, Am. J. M. Sc., 164:173, Aug., 1922.*

The spleen atrophies in inanition. It is an unusually variable organ. Its weight in proportion to body weight varies not only in genera and species, but also in the individual. It changes its volume on slight provocation, and is highly susceptible to hypertrophy and atrophy. In adult dogs complete removal of the external secretion of the pancreas was obtained by resection of the duodenal portion of the gland, tying off securely the severed ends of the remaining pancreas, or by double ligation of the pancreatic ducts. This also led to an excessive decrease in the size of the spleen. However, the shrinkage of the spleen under these conditions can be explained as due to the inanition resulting from the exclusion of the pancreatic juices from the intestine and does not require for its elucidation the postulation of a specific pancreatic splenic interrelationship.

The greatest loss of weight both of the body and of the spleen occurs within the first month. Diminution in weight of the spleen is especially rapid during the first few days of inanition. Observations made on a dog with a pancreatic fistula showed that even if an animal loses over half the amount of pancreatic juice secreted and yet maintains a stationary body weight there is no loss in the size of the spleen. Data were collected on dogs with pancreatic fistulas complicated by infection. Save for a more acute and marked loss in weight of the animals, the results seemed entirely comparable with those obtained in the cases of fasting and removal of the external secretion of the pancreas. Why must the spleen give so readily and lavishly of its substance for the nourishment of its host? Does it imply that this unique gland can play but a slightly important part in the general economy and physiology of the organism; or may it be that the spleen can give heavily of its substance in famine and yet remain a valuable organ? Or does the spleen with specific purpose aid in the garnering and temporary storing of protein food materials in order that it may deal out sustenance when the body needs it?

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**Some Adjuvants of Peptic Digestion.**

*Félix Ramond, Bull. Acad. de méd., Paris, 88:76, July 18, 1922.*

For his experiments on artificial digestion the author used standard test-tubes filled with 5 c.c. 3% gelatin solution, to which are added 25 mg. thymol as preservative, and 5 c.c. of a solution containing 5 parts hydrochloric acid and 1.5 pepsin per 1000. At 15° C., gelatin is digested to a height of 5-6 mm. in 24 hours. Salts derived from various acids, and particularly from hydrochloric and phosphoric acids, were chiefly studied. The addition of chlorids produces an exaggerated digestion, measured by 1, 4 and 5 cm. gelatin respectively in the case of the sodium, magnesium and calcium salts. On the other hand tubes containing tribasic sodium, magnesium or calcium phosphates were scarcely digested at all. From this it is concluded that chlorids are

indicated in hypopepsia and phosphates in hyperpepsia. Studies made of the products of normal digestion of gelatin in vitro showed the presence of amino-acids representing 3% of the total nitrogen. When a few centigrams of chlorids are added this proportion is increased to about 5.4%. Similar experiments made with the digestion of egg albumin in vitro confirmed these results.

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**Comparative Researches on the Efficiency of the Secretions of the Digestive Tract.**

*Katsumi Haramaki, Biochem. Ztschr., Berlin, 129:503, May 23, 1922.*

The mucosa of the gastro-intestinal canal has been examined frequently for secretins and other hormones. Experiments were undertaken to determine whether a secretin for the gastric glands is furnished only by the pyloric mucosa or also by the mucosa of other parts of the digestive canal. Further, comparative quantitative examinations were made to show which mucosal sections contain most secretin for the stomach. It was shown that the mucosa of all investigated sections of the gastro-intestinal tract contain secretin for the stomach. Experiments in which secretin was administered orally proved that in this case also a secretin action is displayed, though to a lesser degree. In subcutaneous injection of secretin solutions, those prepared from the mucosa of the fundus, duodenum and rectum acted equally strongly; the one prepared from the mucosa of the large intestine was hardly less effective and only that prepared from the jejunum was a little weaker. In the oral experiments likewise, secretin solution prepared from the jejunal mucosa was found to be weakest.

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**The Effect of Histamin on the Secretion of the Digestive Juices in Man.**

*Carnot, Koskowski and Libert, Polska gaz. lek., Cracow, 1:531, June 25, 1922.*

The effect of histamin on the secretion of the digestive juices in man has hitherto never been studied. The experiments performed by the authors were to determine this effect, and the quantitative and qualitative changes in the secretions. They observed an increase in the amount of gastric secretion following the injection, and also in the total and free gastric acids. They also studied the digestive properties of the gastric juice, and found that the histamin increased the proteolytic capacity.

Later experiments were performed to determine whether or not this substance also has an effect on the secretion of the other digestive fluids. It is difficult to judge whether or not histamin stimulates the secretion of duodenal, fluid, bile and pancreatic juice, when the Einhorn method is employed. The amount of the fluid excreted differs with the individual; and the same individual may secrete varying amounts at different times. Furthermore, a fluid is sometimes obtained from the duodenum which actually originates in the stomach, which is excreted

under the influence of histamin, and is easily eliminated by way of the pylorus. Numerous observations have established a marked increase in the gastric and pancreatic fluids.

When 1.75 mg. doses were used, the authors never observed serious injuries. The subcutaneous injection was promptly followed by more or less marked reddening of the face, sometimes by headache, and slight palpitation of the heart. The objective symptoms included reddening of the abdominal surface, the chest, the upper and lower extremities, and moderate increase in the rapidity of the heart beat. All these manifestations disappeared after a short period.

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**The Relation of Histamin to Intestinal Intoxication. II.  
The Absorption of Histamin from the Intestine.**

*Jonathan Meakins and Charles Robert Harington, J. Pharmacol. & Exper. Ther., 20:45, Aug., 1922.*

The rate of absorption of histamin from the intestine, as measured by the rate of fall of blood pressure, was greatest from the ileum, somewhat less from the duodenum, and very much less—though still perfectly definite—from the cecum and stomach. Absorption experiments with an Eck fistula indicate that the liver exercises a protective function, probably more mechanical than chemical, against heavy doses of histamin. With the mucous membrane damaged by cutting off the blood supply for 5-15 minutes, the fall of blood pressure would indicate that absorption takes place at first with a rush and then almost ceases.

**METABOLISM**

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**The Significance of Colostrum to the New-Born Calf.**

*Theobald Smith and Ralph B. Little, J. Exper. Med., 36:181, Aug. 1, 1922.*

The difficulty experienced in keeping calves alive which had not received colostrum from the mother led the authors to investigate the effect of withholding this first milk. In order to balance as far as possible the many unknown factors entering into the undertaking, 2 experiments were carried on simultaneously. One group of calves was to have colostrum, the other not; the calves were obtained from the same large herd.

The group of 10 calves taking colostrum survived the danger period and were kept various periods of time thereafter; 3 died unexpectedly after 25, 38, and 45 days respectively. The protocols indicate that death was most probably due to some kind of poison, the evidence being quite conclusive that there was no ordinary infection involved. A condition common to all 3 animals was the presence of punctiform hemorrhages throughout the intrathoracic portion of the thymus. Of the second group of 12 calves which received no colostrum, 9 died and 3 survived; 7 died within 6 days. The appearances at autopsy differed somewhat from animal to animal and were due to differences in blood content of the organs, resulting in varying degrees of congestion. Bacteriologic study revealed identical conditions in all these animals. The spleen, liver

and kidneys contained large numbers of *Bacillus coli*. Other organs were not cultured except in several cases certain joints which also yielded *B. coli*.

The data presented permitted certain definite inferences. The calf deprived of colostrum lacks something which permits intestinal bacteria to invade the body and multiply in various organs, the rapidity and duration of which determine the fate of the calf. In most cases a rapidly fatal septicemia results. When the resistance is greater life may be prolonged or the animal survive indefinitely. In general it may be concluded that the function of colostrum is essentially protective against miscellaneous bacteria which are harmless later on when the protective functions of the calf have begun to operate and accumulate energy.

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**Nutrition during Mental Work.**

*Kestner and Knipping, Klin. Wchnschr, Berlin, 1:1353, July 1, 1922.*

The authors investigated the gaseous metabolism during mental work by means of Benedict's respiration apparatus, all voluntary muscular activity being excluded as far as possible. The mental work consisted in making an abstract of a difficult scientific treatise, which was read aloud. The experiments showed without exception increased oxygen consumption. But the increased calory requirement for mental work is very inconsiderable as compared with that for even slight physical exertion, indicating that the mental worker does not require much food. But the experiments also showed in all cases greater increase in oxygen consumption than in carbon dioxid excretion, i. e. a decrease of the respiratory quotient. Cerebral activity evidently causes some acid to enter the blood, by which the carbon dioxid is expelled.

Suspecting this acid to be phosphoric acid, the authors investigated the phosphoric acid content of the blood under the same experimental conditions and succeeded in demonstrating a regular increase of phosphoric acid during mental exertion. This acidification of the blood must be counteracted, and this can only be effected by the secretion of gastric juice, which alters the reaction in the alkaline direction. Since meat induces the most abundant and the most prolonged secretion of gastric juice, the mental worker requires a liberal meat diet.

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**The Influence of Operative Intervention on the Central Nervous System on Total Metabolism and Protein Metabolism in Warm-Blooded Animals.**

*H. Freund and E. Grafe, Arch. f. exper. Path. u. Pharmakol., Leipsic, 93:285, June 23, 1922.*

The results formerly obtained by the authors in regard to heat regulation in animals by transection of thoracic and cervical portions of the spinal cord, are confirmed by experiments on 10 dogs. Division of the thoracic spinal cord causes easier undercooling with fully normal resisting capacity to overheating. The regulatory increase of metabolism at external temperatures, that only just avoid leading to undercooling, rises to twice the normal value. In division of the cervical spinal cord, the capacity for resistance to undercooling and overheating is lost; body temperature becomes a function of external temperature. Following

the administration of food, adrenalin or salicylic acid, temperature rises take place through increase of peripheral metabolism.

Concerning the alteration of albumin metabolism, in division of the thoracic spinal cord, the percentage participation of albumin in the total calories diminishes, while the total metabolism of the animals is increased; after division of the cervical spinal cord at the seventh or eighth cervical vertebra, the nitrogen value per kilo is doubled, while the percentage participation of albumin in the production of calories rises to the same extent. With excessive carbohydrate supply (100-150 glucose) albumin decomposition may become restricted. In these animals adrenalin induces a decrease in the high urinary nitrogen values, because adrenalin increases nitrogen elimination from a central attacking point, whereas in division of the cervical spinal cord the path from the center to the periphery is barred. From these experiments the authors conclude that the animals' albumin metabolism disturbance is related to their heat regulating capacity and, hence, that there exists a hypothetic albumin center, from which impulses proceed to the liver's albumin depot, which is connected with the heat center.

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**Growth and Reproduction upon Simplified Food Supply. II. Influence of Food upon Mother and Young during the Lactation Period.**

*H. C. Sherman and Marie Muhlfeld, J. Biol. Chem., 53:41, July, 1922.*

In the authors' experiments breeding rats were fed upon diets containing respectively one-sixth whole milk powder to five-sixths ground whole wheat or one-third whole milk powder to two-thirds ground whole wheat. Young were successfully reared on both diets and each diet may be regarded as adequate for growth, reproduction, and successful suckling of the second generation. The tabulated results show that the larger proportion of milk in the second diet resulted in these evidences of improved nutrition: (1) increase in the number of young produced; (2) increase in the percentage (and therefore also in the number) of young successfully suckled; (3) better maintenance of the body weight by the mother while suckling the young; (4) higher average weight of young at a standard weaning age of 4 weeks; (5) more economical utilization of the calories of food consumed (as well as of the body material of the mother) in the rearing of the young to weaning age.

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**Growth and Reproduction upon Simplified Food Supply. III. The Efficiency of Growth as Influenced by the Proportion of Milk in the Diet.**

*H. C. Sherman and Josephine Crocker, J. Biol. Chem., 53:49, July, 1922.*

Young rats were separated from their mother and placed on any one of certain experimental diets at a standard "weaning" age of 4 weeks, and thereafter weighed on a regular weekly weighing day. Each diet was tested 30-39 times and upon 129-164 rats. The efficiency of growth as influenced by diet was here studied by determining and com-



paring the gains in weight per 1000 calories of food consumed during a fixed period of rapid growth in young rats.

Diet A. One-sixth whole milk powder and five-sixths ground whole wheat with sodium chlorid 2% of the weight of the wheat. Energy value 3.79 calories per gram. Diet B. One-third whole milk powder and two-thirds ground whole wheat with sodium chlorid 2% of the weight of the wheat. Energy value 4.04 calories per gram. Diet C. Equal weights of whole milk powder and ground whole wheat with sodium chlorid 2% of the weight of the wheat. Energy value 4.29 calories per gram. Diet D. Two-thirds whole milk powder and one-third ground whole wheat with sodium chlorid 2% of the weight of the wheat. Energy value 4.55 calories per gram. The animals were supplied distilled water and allowed to eat ad libitum from weighed portions of their respective food mixtures. While Diet A was found to be adequate, the tabulated results show that the remaining 3 diets, containing a greater portion of milk, were more efficient.

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**Dietary Factors Influencing Calcium Assimilation. II. The Comparative Efficiency of Dry and Green Alfalfa in Maintaining Calcium and Phosphorous Equilibrium in Milking Cows.**

*E. B. Hart, H. Steenbock, C. A. Hoppert and G. C. Humphrey, J. Biol. Chem., 53:21, July, 1922.*

The authors' plan was to feed liberally to milking cows dried alfalfa hay plus silage and a grain mixture, over a period of time sufficiently long to establish the assumed negative calcium balance, and then to replace dried alfalfa hay with fresh, green alfalfa in an amount equivalent in dry matter to the dry hay. The animals were confined to metabolism stalls with quantitative collection of the excreta and milk. Calcium determinations were made on all feeds, milk, and excreta by the McCrudden method. Phosphorus was determined in feeds, milk, and feces after ashing in the presence of magnesium nitrate. In the urine phosphorus was determined by the Neumann method, i. e. after oxidation with nitric acid in the presence of sulphuric acid. The hay consumption was 10 lb. per animal per day. The tabulated results show that on fresh green alfalfa more liberal storage of calcium was observed with these animals than on dry alfalfa hay. With positive calcium balances there were also positive phosphorous balances with the 3 animals under observation. The authors believe the question whether positive or negative calcium balances will prevail in liberally milking cows through the use of such an efficient carrier of calcium as alfalfa hay is determined by the quality of the alfalfa hay used. By "quality" is meant the relative degree of destruction in the curing processes of the unknown factors affecting calcium assimilation.

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**The Fate of Certain Sulphur Compounds when Fed to the Dog.**

*Carl L. A. Schmidt and Guy W. Clark, J. Biol. Chem., 53:193, July, 1922.*

The authors' experimental work was carried out on dogs which were kept on constant diets containing a low but not a minimal amount

of protein. The dosage of the particular substance was added to a part of the food which was fed first. The tabulated results show that taurin is excreted in the urine unchanged and not as taurocarbamic acid, as others have thought. Cysteic acid is deaminized, but the remainder of the molecule is excreted in the urine unchanged. Administration of isethionic acid is not followed by an increase in urinary sulphate, the authors found, nor is the urine a channel for the elimination of bile acids when the latter are fed. With the exception of large doses of sodium thiosulphate the ingestion of the various sulphur compounds under consideration did not lead to the appearance of appreciable amounts of sulphurous or thiosulphuric acid in the urine.

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**The Effect of a High Protein Diet on the Blood Catalase.**

*W. E. Burge and J. M. Leichsenring, Am. J. Physiol., 61:574, Aug. 1, 1922.*

The object of the present investigation was to determine if the ingestion of a large meal of meat would increase the blood catalase corresponding with the increase produced in metabolism, and if the ingestion of large quantities of meat for several successive days would produce an increase in catalase corresponding with the rise in basal metabolism. Dogs were used in the experiments. The catalase determinations were made by adding 1 c.c. of the jugular blood to 25 c.c. of neutral hydrogen peroxid, and the amount of oxygen liberated in 10 minutes was taken as a measure of the catalase of the blood. Determinations were made of the catalase of the blood of the dogs on basal metabolism while they were being kept on a mixed diet as well as on a diet consisting solely of a large quantity of meat. It was found that the ingestion of a large meal of meat produces an increase in catalase parallel with the increase produced in metabolism. The ingestion of large quantities of meat for several successive days increased catalase corresponding with the rise produced in basal metabolism.

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**A Comparison of the Nitrogenous Metabolism during Single and Fractional Feedings.**

*Alfred Chanutin and Lafayette B. Mendel, J. Metab. Research, 1:481, April, 1922.*

The effect of the administration of the day's food in a single and in divided portions on metabolism was studied. The literature discloses conflicting claims in the latter respect and the results of investigations of protein metabolism show inconsistencies. Accordingly the authors undertook experiments on the effect of partition of diets both poor and rich in protein on metabolism. The experimental animals were 3 female dogs which were kept in metabolism cages on a diet of commercial casein, lard, butter fat, dried yeast, sugar, bone ash and a salt mixture. The composition of the total diet as to caloric value, nitrogen, salts, vitamins, etc., was constant. This diet contains a suitable protein and vitamins A and B. Water was supplied ad libitum. The animals were catheterized once daily and the feces marked off by carmin. The urine's

and feces' total nitrogen content was determined by the Kjeldahl-Gunning method. Three experimental periods were maintained, each commencing as soon as the daily nitrogen output became constant. During the first and third periods the food was consumed in a single meal, during the second period it was divided into equal portions, each of which was fed at intervals of 1½ hours spread over 12 hours. The results, recorded in tables, do not reveal any significant variations to arise from fractional feeding.

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**Irritative Uric Acid.**

*Bruno Mendel, Klin. Wchnschr., Berlin, 1:1261, June 17, 1922.*

Joel observed that after repeated small meat feedings, not only all of the uric acid corresponding to the purin content is eliminated, but also an excess derived from the endogenous store, and that this represents the product of a stimulus incited by the food. The author points out, however, that purin-free protein feeding increases the elaboration of uric acid and induces a rapidly diminishing leukocytosis. He believes the subsequent leukocyte disintegration represents the source of the excess uric acid. Adrenalin and pilocarpin injections have the same action, namely leukocytosis followed by disintegration of leukocytes and excess of uric acid. But the intense uric acid excretion after atophan is brought about by primary leukocytolysis without previous leukocytosis.

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**Animal Calorimetry. XXII. The Production of Fat from Protein.**

*H. V. Atkinson, David Rapport and Graham Lusk, J. Biol. Chem., 53:155, July, 1922.*

In the authors' metabolism experiments on dogs, an additional procedure to that employed in the previous experiments was added. The standard diet, containing 70 gm. of starch was given every evening at 5 P. M. in order to change the glycogen reservoirs of the body. The authors found that when the glycogen reservoirs of the body are low the ingestion of meat in large quantity results in the deposition of glycogen. The continued ingestion of much meat brings about the retention in the body of a pabulum consisting partly of glycogen and partly of fat. Only when meat in very great excess is given, is fat alone retained. When a carbohydrate-containing meal is given in the evening and 1000 gm. of meat in the morning, then during the height of protein digestion the respiratory quotient indicates a production of fat from protein. Following the prolonged ingestion of meat in large amounts, which induces the retention of "deposit protein," the basal metabolism may rise from a former level of 16 calories per hour to one of 19.7 from which level it slowly falls with the gradual elimination of "deposit protein."

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**Fat Excretion.**

*Elsie Hill and W. R. Bloor, J. Biol. Chem., 53:171, July, 1922.*

In this work cats were used and feedings experiments were carried out on them with 2 fats of widely different composition and the

feces fat examined. The animals were given a basal diet which was a practically fat-free mixture of starch and extracted casein with meat extract for flavoring and bone ash to provide bulk. Experiments were conducted with (1) a diet of lean meat, (2) the basal diet alone, (3) the basal diet plus olive oil, (4) the basal diet plus coconut oil; in every case making the amount of the daily food such as to supply 100 calories per kilo of body weight. Each experiment lasted a week, the periods being marked off by charcoal. The tabulated results show that when moderate amounts of fat are fed the fat of the feces is largely independent of the diet, and in composition approaches that from a fat-free diet. Feces fat cannot ordinarily be regarded as unabsorbed food fat and, therefore, feeding experiments as a test of the extent of utilization of food fat are of doubtful value unless account be taken of the amount and kind of fat which appears in the feces independently of the food.

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**Lipoids.**

*H. Iscovesco, Presse méd., 30:653, Aug. 2, 1922.*

Lipoids belong to the group of "adipoid" substances, which includes also true fats, fatty acids, waxes, cholesterids, protagons and cerebro-sids. The molecule of lipoids contains one or several higher fatty acid radicals, a variable nitrogen base, and sometimes sulphur, with or without phosphorus.

Lipoids are not colloids, although they may give fine emulsions in water. A number of facts are known concerning their rôle in immunity, but these cannot be synthetized into a general law.

Numerous researches have shown that lipoids are indispensable to life and growth, and it seems that the organism in this respect has not only quantitative but also qualitative needs. The author's researches have shown furthermore that certain lipoids possess the power to influence particular organs. It is recalled in the first place that the heart, liver, placenta, corpus luteum, brain, thyroid, etc., contain specific lipoids. The administration of these is in a general way followed by a hypertrophy and increased functional activity of the corresponding organ. Iscovesco has in particular isolated from the liver a lipid which both stimulates this organ and has a remarkable action on the growth and weight of animals. He has also shown that the vitaminic properties of cod-liver oil are due to the hepatic lipoids which it contains. To understand the mechanism of the action of lipoids it should be remembered that the quantity of these substances contained in various organs generally diminishes when they are diseased, and also that when a lipid is administered to an animal it is fixed electively by a precise organ. The administration of sahidin, for instance, which is a lipid of the nervous system, is followed by an increase of the lipoidic phosphorus contents of the brain, which apparently fixes the greater part of the sahidin supplied, to the exclusion of other organs such as the liver. Experiments have also shown that in certain cases our organs are no longer able to synthesize their own lipoids. These various considerations have led the author and others to use lipoids for therapeutic purposes, and particularly good results have been obtained with ovarian lipoids in various conditions due to a deficiency of the ovary. The

lipoids of red blood-cells, of the brain, kidney, pancreas, etc., have also obvious indications. Hepatic lipoids are now used with success by many physicians in place of cod-liver oil.

It must be admitted that many cases of deficiencies of internal secretions are merely due to a deficiency of certain lipoids, which should be supplied ready made. This homo-alimentary conception finds also some support in the fact that albumins are all the better utilized by the organism as they come from a more nearly related animal species.

The existence of vitamins A is very doubtful, but if they do exist, they are chiefly found in the lipoids of the liver and pancreas. There are vitamins which favor the growth of the entire organism and also local vitamins for each organ, which are its lipoids. It is possible that the specificity of the lipoids of different organs is due to their nitrogen base.

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**The Lipoid Metabolism of the Male Genital Glands.**

*Konrad Kleinicke, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:185, 1922.*

The author examined 24 testicles, selected at random, to determine whether, as was shown by Leupold for cholesterol, other testicular lipoids can also be resorbed without injury to the seminal cells. Frozen formol sections were examined with hematoxylin, eosin, scarlet, and Nile-blue sulphate, as well as by the Smith-Dietrich and Tischler methods; in addition double refraction was tested. The injuries from various diseases consisted either in only slight shedding of seminal epithelium or in abundant desquamation with partial transformation of Sertoli's cells into cylindric forms, more or less progressive replacement of the seminal epithelium by Sertoli's cells and finally thickening of the tubule walls on the internal surface of which heavy hyaline deposits developed in advanced cases. The parts that stained red with Nile-blue were the same as those showing double refraction (disappears on warming and recurs on cooling): they were entirely absent from the interior of the seminal tubules and were also less numerous in the interstitial cells than the other lipoids. The substances that stained dark brown to brownish black by the Smith-Dietrich method should probably be regarded as phosphatids, owing to the invariably negative result of the Tischler staining, but possibly cerebroside and cholesterol and fatty acid mixtures were also involved. The parts stained dark blue by Nile-blue probably contained cephalin (no fatty acid nor soap; Tischler staining negative). In slight injury the seminal epithelium contained fewer cephalins than lipoids; in the interstitial cells the phosphatids were nearly always increased as compared to other lipoids. Cholesterol esters were not detectable at all morphologically within the seminal tubules, in the interstitial cells of slightly injured testicles only in traces, in severely injured ones usually abundantly, but they may also be present in small amount or may be entirely absent. Cholesterol esters and cephalins seem to supplement each other and their total obviously corresponds to the substances stainable by scarlet. As the lipoid content is sometimes slight in severe injuries, while in moderately severe injuries the lipoid content may be very abundant, the abundance of lipoids is probably also determined by the rapidity of their removal. With a thickened tubule wall the resorption from the tubules into the



interstitial cells is rendered more difficult and the tubules then contain lipoid in abundance owing to congestion even in only slightly advanced degeneration.

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**Frog Tadpoles as Biologic Agents for the Study of Vitamins.**

*G. Billard, J. de physiol. et de path. gén., Paris, 20:182, No. 2, 1922.*

Frog tadpoles were selected for the tests because they are easily obtainable, vigorous and resistant, undergo transformation with widely varying diets and are readily subject to observation. The presence, in the water with them, of green algae of the genus *Scenedesmus* is essential. The algae are unquestionably eaten by the tadpoles, but appear intact in the feces. However, they may be altered minutely. The water in which the tadpoles are kept should be changed every day or two, both to promote the health of the tadpoles and to prevent the algae from invading the laboratory, with consequent vitiation of various tests. The tadpoles' diets were vegetable and animal. Crushed leguminous seeds (beans, peas, lentils) permitted complete metamorphosis in 9 weeks, haricots produced death in 7 days, probably because of cyanids. Crushed wheat, barley and rye were favorable, oats killed in 9 days. Metamorphosis was prevented by feeding with cereals from which the growth vitamins had been removed.

The albumen of cooked eggs produced death in a month. Development was slowed by combined egg albumen and beef fat. Combined egg albumen and wheat starch slowed growth, causing circular movements due to incoördination. The condition suggested beriberi and rickets. Combined starch, egg albumen and beef fat produced true fluid dropsy in 2 weeks, without meteorism. Death occurred very soon, the peritoneum and skin bursting, the condition resembling the large abdomen of children fed with fat soups. Protein does not appear to be digested. The algae grow with difficulty in water containing it; when they grow well the tadpoles do not die. Combined protein and fat are favorable for the algae, but slow the frog growth, which, however, progresses in time if algae are added to the diet. Here a new element seems to replace the growth vitamin. There is symbiosis of the tadpoles, algae and bacteria. The avitaminous diets produce curious caudal deformities, curable with wheat bran. The tadpoles clearly have an appetite for the algae, this appetite affecting their digestive juices.

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**The Knowledge of Accessory Foods. The Influence of Diet Deficient in Fat and Cholesterin on the Growing Organism.**

*Ph. Niemes and Leonhard Wacker, Arch. f. exper. Path. u. Pharmacol., Leipsic, 93:241, June 23, 1922.*

Gray-black rats were fed (1) one lot with whole milk powder, starch and water; (2) another lot with skim milk powder, starch and water; (3) a third lot with the second type of diet and cholesterin; and (4) a fourth lot with the first type of diet and cholesterin. The mixture was always prepared with a constant calorific value. Results showed that the animals fed on whole milk mixture developed normally;

that those fed on skim milk died the earlier the younger their age at the commencement of the experiment. When cholesterin was added to this diet they died even sooner under extreme emaciation. From this the authors conclude that a vitally important substance must be present in milk fat. Cholesterin itself is nonpoison as shown by experiments in which cholesterin was added to the whole milk mixture. These animals developed normally.

The gray-black rats fed on skim milk-starch mixture turned brown within half a year and on returning to a normal diet the skin's original color was slowly restored. The gait of the skim milk animals was spastic, the vertebral column kyphotic, but no anatomic alterations were detectable in bones or muscular or nervous system. Gas formation, as a sign of carbohydrate fermentation, was found in stomach and intestine of animals fed on skim milk, but the cause of death cannot be referred to gas formation. Skim milk animals showed a tendency to infections, particularly to inflammation of the eyelids and pneumonia. Addition of cholesterin to whole milk feeding did not promote growth.

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**Studies on Qualitative Undernutrition. II. Experimental Detection of Antineuritin.**

*Franz Hofmeister, Biochem. Ztschr., Berlin, 129:477, May 23, 1922.*

Beriberi produced in birds by polished rice may be obviated by supplying rice-bran or yeast. Hence it is clear that these substances contain something indispensable for life which is wanting in polished rice. If this unknown something, which American experimenters have named vitamin B, be added to the polished rice in feeding, a complete food is formed. This vitamin B could not be hitherto isolated chemically. Experiments were undertaken to authenticate antineuritin in beriberi rats. First of all it was to be proved that antineuritic extracts unfold protective or curative effects in them. Rat beriberi could be produced with relative ease: curative attempts in the final paralytic stages have been constantly unsuccessful. On the other hand, the administration of antineuritin in the atactic stage has a magical effect. The continuous recedence of atactic and spastic symptoms following administration of a preparation with otherwise unchanged vitamin-free nutrition proves conclusively that the preparation contains antineuritin. A further proof is the effect on the weight curve in the prodromal stage, in the light of the fact that atactic and spastic phenomena do not set in thereafter or do so only correspondingly later. Regarding the origin of the antineuritin preparations inducing the curative action no details are communicated.

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**Organic Foods with Specific Action. XIII. The Deficient Oxygen Supply of the Cells as the Cause of the Symptoms of Alimentary Dystrophy in Pigeons.**

*Emil Abderhalden and Ernst Wertheimer, Arch. f. d. ges. Physiol., Berlin, 194:647, June 12, 1922.*

In order to analyze the fall of temperature in dystrophic animals, gas exchange experiments were undertaken which showed considerable

lowering of gas metabolism in the whole animal as well as in isolated cells and tissues. It was found, at the same time, that those substances which are capable of removing the dystrophic symptoms also increase cell respiration. Obviously the oxidizing processes are restricted in one-sided nutrition, which also causes the nervous symptoms, inasmuch as acute disturbances in the oxygen supply to the spasm-centers induce slowly resulting paralyses. Hepatic necroses may probably be interpreted similarly. In addition to this the oxidations are impaired by the diminution of red blood-corpuscles and of their hemoglobin content. A normally nourished pigeon reacts to oxygen deficiency differently from one fed for a long time exclusively on polished rice. The latter shows signs of dyspnea much sooner and also recovers less rapidly when air is supplied than the normal animal. A series of such experiments, in which oxygen deficiency was produced by evacuation, was performed. W. R. Hess has confirmed the findings regarding disturbances of oxidation by staining methods and has compared them with those observed in hydrocyanic acid poisoning. To decide the question of whether alimentary dystrophy and hydrocyanic acid poisoning are identical in this respect, certain problems must be solved: (1) How does total metabolism behave in hydrocyanic acid poisoning? (2) How does tissue respiration behave under these conditions? (3) What influence has yeast extract on the respiration of such animals? (4) Is yeast extract capable of increasing resistance to hydrocyanic acid poisoning? Yeast preparations possess no influence on cyanid poisoning. Further, gaseous exchange increases, often very considerably, as soon as the characteristic poisoning symptoms appear. Tissue respiration (brain, muscle, liver) is not lowered considerably in cyanid poisoning, nor can it be increased by yeast extract. Also, pigeons fed on polished rice are not necessarily more sensitive to cyanid poisoning than normal ones. Therefore, no similarity exists between cyanid poisoning and dystrophy. In the respired air of the affected pigeons (fed on rice) acetone is detectable, which, like the presence of tyrosin and leucin in the stools, points to disturbance of oxidation. Similar conditions might prevail in diabetes. As a matter of fact, erythrocytes of diabetics barely respire, whereas under addition of yeast extract or yeast autolyzate their respiration increases rapidly. The regular occurrence of disturbed cell respiration in diabetes is of great significance.

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**The Metabolism of Pigeons Deprived of Vitamin B.**

*F. Caridroit, J. de physiol. et de path. gén., Paris, 20:189, No. 2, 1922.*

The author has studied the metabolism of 4 pigeons, 1 being used as check. The avitaminous diet consisted of polished rice. The 4 pigeons died in 3-4 weeks. The respiratory intensity remained nearly constant during the first week, then fell considerably, indicating diminished metabolism. The respiratory quotient was at first 0.9, fell to 0.7 and rose again to 0.8 on the appearance of symptoms. The nitrogenous excretion was greatly diminished. The injection of histamin prevented symptoms, but did not appreciably modify the respiratory metabolism. 0.42 mg. were injected into one of the test pigeons every day. The

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fluctuations in the respiratory quotient are probably due to successive burning of the body carbohydrates, fats and proteins. The quotient probably cannot fall as low as indicated by Ramoino, which would presuppose an oxygen reserve.

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**Studies on Experimental Rickets. XXII. Conditions Which Must be Fulfilled in Preparing Animals for Testing the Antirachitic Effect of Individual Foodstuffs.**

*E. V. McCollum, Nina Simmonds, P. G. Shipley and E. A. Park, Bull. Johns Hopkins Hosp., 33:296, Aug., 1922*

The purpose of this paper is essentially cautionary, to point out in detail the discretion which must be used in dietary tests of substances influencing bone growth. Specifications are given for the preparing of proper grains and leafy vegetables, for the purification of casein, selection and analysis of gelatin, preparation of butter fat, and the use of commercially analyzed inorganic salts. Workers are warned against accepting the data on labels of manufacturers of chemicals, which are not always reliable. The need for care in preparation of the test diets is further illustrated by report of experiments in which 9 lots of rats were given diets identical as to protein, fat soluble A, water soluble B, and the unnamed bone-controlling substance (cod-liver oil vitamin). The diets were all equally deficient in fat soluble A. Relatively slight differences in the inorganic salts were brought about in these otherwise identical diets. According to the proportions of the inorganic salts, the rats' bones showed conditions varying from normal to very severe rickets. Therefore experimentors must use great care in preparing and analyzing their diets, to avoid such slight variations. As an accidental observation, it was found that calcium given as lactate proved less satisfactory for promoting bone growth than calcium carbonate.

**RESPIRATORY SYSTEM**

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**The Lipoid Content of the Suprarenal Cortex of the Guinea-Pig in Experimental Scurvy.**

*Peiper, Klin. Wchnschr., Berlin, 1:1263, June 17, 1922.*

Guinea-pigs fed exclusively on oats for 6-8 weeks succumb to scurvy. While the cortical lipoid content is considerable in cachexia and inanition the scorbutic suprarenal cortex shows intense lipoid impoverishment shortly before or after death, which is however not uniform, there being small lipoid bodies in patches. Death supervenes simultaneously with lipoid exhaustion. If a scorbutic guinea-pig be again fed on green food an enormous overloading of the cells with lipoid takes place similar to that observed in artificial feeding or cholesterol injection in normal animals. This lipoid is first given off to the outermost cortical cells after the maximum filling of which the central trabecular cells immediately adjacent to the vessels are supplied. This observation is opposed to the theory that the formation of suprarenal lipoids is associated with the cell granules.

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**The Effect of Section of the Vagi on the Respiration of the Cat.**

*J. Trevan and E. Boock, J. Physiol., London, 56:331, July 21, 1922.*

In the authors' experiments cats, anesthetized with ether and tracheotomized, were decerebrated with Sherrington's guillotine and the remainder of the cerebrum was removed with a scalpel. Respiration was recorded by a string stitched to the abdominal wall and run over a pulley to a lever. The results have been recorded graphically and show that the response of the center to section of the vagi depends on the level of the section through the brain stem. Cats with the brain removed in front of the anterior colliculi and at right angles to the neural axis, resemble normal animals in their response to section of the vagi, alteration of the reaction of the blood, injection of acetyl acetone, etc. Very lightly anesthetized animals may show little or no change in the respiratory movements on section of the vagi. With a section passing between the colliculi, the response of the animal to section of the vagi consists of slowing and slight deepening of the respiratory movements. When the section passes posterior to the posterior colliculi, the stimulation by acetyl acetone gives place to a depression and the sensitivity to acid is much depressed. The effect of division of the vagi is to produce incoördinated inspiratory gasps. The authors make the tentative suggestion that the part of the respiratory center remaining in an animal decerebrated just behind the anterior edge of the pons is a representative of a more primitive type of center, in which the adaptation of the respiratory movements to the needs of the body depends more on vagal stimuli and less on the composition of the blood, than is the case in the more highly developed center of the normal cat.

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**Anoxemia and the Administration of Oxygen.**

*N. Morris, J. Physiol., London, 56:283, July 21, 1922.*

The objects of the present research were (1) to determine the variations in the oxygen content of the blood in varying degrees of interference with the pulmonary ventilation, (2) to ascertain to what extent the oxygen content of arterial blood might be decreased without marked interference with the processes of oxidation in the tissues, (3) to study the influence of oxygen administration in cases of interference with the pulmonary ventilation. The experiments were performed on cats under a constant degree of ether anesthesia. Samples of blood were withdrawn simultaneously from the left carotid artery and left jugular vein into syringes containing neutral potassium oxalate, before and after asphyxia of varying degrees had been induced in the animal. The tabulated results show that up to a certain degree of asphyxia the amount of oxygen in the arterial blood exceeds that in the venous. The head of oxygen, however, varies within wide limits. When the asphyxia becomes more intense the percentage oxygen saturation in the arteries begins to fall much more rapidly than in the veins and in the extreme stages of asphyxia the venous blood actually contains a higher percentage of oxygen than does the arterial. These results indicate that the arterial and venous oxygen contents do not run



parallel as has been maintained by some observers. To determine the effect of position in the venous system on the oxygen content of the venous blood, simultaneous puncture of the right ventricle and the left jugular vein was performed. This was accomplished with the thorax opened and respiration maintained by a motor pump. The tabulated results show the blood from the right ventricle to be always more unsaturated than that from the jugular vein. The author also found that a pneumococcal infection, while it produced a lowering of the percentage saturation of the blood, did not cause a fall in its total oxygen capacity. Unilateral interference with the pulmonary mechanism such as induction of unilateral pneumothorax or occlusion of one bronchus produced a fall in the oxygen saturation of the blood both arterial and venous, but a small increase in the head of oxygen. Interference with the respiratory exchange in both lungs as produced by injection of histamin or partial blocking of both bronchi and induction of asphyxia led to a decrease in the arterial oxygen saturation and a fall in the head of oxygen. Administration of oxygen subsequent to interference with the pulmonary mechanism raised the oxygen saturation of the arterial blood to normal level. Oxygen administration antecedent to the induction of pneumothorax and continued thereafter prevented any fall in the oxygen saturation of the arterial blood.

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**A Comparative Study of the Different Methods of Artificial Respiration.**

*R. Burton-Opitz, Am. J. Physiol., 61:562, Aug. 1, 1922.*

The author made a comparative study of the different methods of artificial respiration, employing for the purpose a very delicate spirometer which he devised. He criticizes most of the standard methods of artificial respiration and finally recommends the following modification of the method of Howard: The hands should be placed upon the hypochondriac and epigastric regions, so that the tips of the thumbs come to lie below the xiphoid cartilage, while the fingers are extended laterally across the lower ribs. The carpal margins of the hands may then be used to exert pressure upon the organs occupying the upper extent of the abdominal cavity. The compression should not be made in a direct line inward but inward and upward, because the principal path of attack is through the diaphragm. Lastly, the legs should be slightly flexed upon the trunk, so as to facilitate this particular manipulation. If these modifications are made, it is possible to equal about two-thirds of the volume of the normal tidal air.

**NEUROMUSCULAR SYSTEM**

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**Tactile Sense and Pressure Sense, Particularly Deep Pressure Sense.**

*Theodor Hausmann, Arch. f. d. ges. Physiol., Berlin, 194:611, June 12, 1922.*

Frey's theory of the similarity of tactile sense and pressure sense was contradicted by the experiments of Head, who after dividing the lateral cutaneous antebrachial nerve observed anesthesia in the anes-

thetic region for tactile stimuli but not for pressure stimuli, which latter persisted even after freezing the anesthetic region with ethyl chlorid. Doubts have been cast on Head's assertion of 2 sensibilities with separate perceptive and conductive apparatus; Frey has stated that the stronger pressure is perceived by propagation to peripheral sensitive-efficient cutaneous regions. He relies chiefly on Hacker's experiments with circular freezing in the anesthetic region, in which the pressure threshold is increased sixfold. However, Hausmann maintains that Frey's conclusion is inadmissible because it proceeds from the erroneous assumption of an unaltered pressure sense in the frozen region. Thus, the quality of the blood supply has a material influence on tactile sensibility. Frey's other arguments also point merely to the possibility of a peripheral propagation of the pressure stimuli, without refuting Head's theory. That theory is supported, above all, by pathologic experience (Strümpell and others). The author has observed cases of war injuries that agree partly with Head's experimental conditions and partly with Strümpell's observations, which can only be explained by interruption of nerve tracks conveying deep pressure-sense. On a raised cutaneous fold, it is true (here Frey is right), pressure sense is not abolished. Peripheral propagation of pressure is there not possible. If a cutaneous fold be raised in nervous patients in such a manner that it falls partly within the anesthetic and partly within the intact region it is insensitive to pressure in the anesthetic part. On the other hand, the same portion of skin is sensitive to pressure if it lies flat. Thereby the existence of a deep pressure sense and pressure sense of the skin must be distinguished. In addition there exists the deep pressure sense from which originates the excitation of the receptor apparatus of sub-cutaneous structures. Tactile sense might very well be produced even without deformation, for instance, by perception of the substitution of contact with air for that with another body. The change of the contact medium is perceived. Deep pressure sense is surely not, as was thought by Sherrington, confined to the musculature, as it exists also at the finger pad.

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#### Visceral Sensibility.

*Fröhlich and Meyer, Klin. Wchnschr., Berlin, 1:1368, July 1, 1922.*

The authors have clearly demonstrated by numerous experiments that, in dogs, the fibers which conduct sensations of pain related to the bladder, rectum, colon, small intestine, and to the arteries of the extremities enter the central system by way of the posterior roots and therefore have the character of spinal nerve-fibers, although they are intermingled with the vegetative nerves. The anterior roots play no part in the sensation of pain. Sensations of pain are conducted from the bladder by the pelvic nerves to the posterior sacral roots, and from the intestine by the splanchnic and hypogastric nerves to the posterior thoracic roots.

Adequate stimuli for the excitation of pain in the viscera may be induced by stretching and by spasmodic contraction. The pain caused by stretching seems to depend on some small degree of tension of the mesenteric attachment close to the intestinal wall. The colicky pain caused by contracture, on the other hand, may be caused without any

dragging on the mesentery; the authors induced contraction through the intestinal serosa by means of barium chlorid. Intra-arterial injections of barium chlorid in the peripheral direction caused violent vascular pains in dogs, and the same result was obtained with oil of mustard. The arterial spasm induced by adrenalin does not cause pain. The arterial pain is also absent after severing the posterior roots.

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**The Sensibility of the Bladder.**

*William Waltz, Deutsch. Ztschr. f. Nervenheilk., Leipzig, 74:278, June, 1922.*

Apparently the bladder has, even under normal circumstances, a definite sensation when it is moderately distended, stasis, following voluntary closure of the sphincters, being physiologic. Sensations in the bladder, are readily appreciated because its sensibility, is, as a matter of experience, closely associated with voluntary processes. Under normal conditions the sensation of pain in the bladder cannot be tested. The question arose as to whether during operations moderate temperature differences play an important rôle in the production of pain, it being believed that the sensibility to temperature would be some indication as to how far the sensibility of the bladder could be brought into analogy with the sensibility of the skin, on the one hand, and with the sensibility of the other organs, on the other. The sensibility to temperature was tested by allowing to flow into the bladder, by means of a double-walled glass catheter, to exclude the very sensitive urethra, warm and cold solutions of menthol. For determining tactile sensibility, visual contact of the bladder wall with a ureteral catheter, under ureterocystoscopy, was practiced. There was no evidence of sensibility to temperature in the bladder wall. Sensibility to touch was absent in most cases; occasionally, however, it was quite well developed; when present, it was especially common in the region of the ureteral openings. Vagotropic and sympathicotropic substances had no influence on the sensibility to touch. Individual differences in sensibility to touch depend most probably on anatomic variations in the nerve supply.

Sensibility to galvanism was tested by inserting into a ureteral catheter a German silver wire with a knob at the end; this was employed as a stimulating electrode with which the wall of the bladder was tested under visualization by means of a ureterocystoscope. The bladder was regularly found to be sensitive to galvanic stimulation. This sensitiveness was apparently not brought about by muscular contractions, but by direct stimulation of the nerves in the mucosa of the bladder or in the bladder wall itself.

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**Diaphragmatic Tonus.**

*Ken Kuré, Tohei Hiramatsu and Shigeru Sakai, Arch. f. d. ges. Physiol., Berlin, 194:481, May 17, 1922.*

It has been previously shown that division of the lymphatic fibers running from the spinal cord through the splanchnic nerves and the celiac ganglion is followed by depression of the corresponding half of

the diaphragm. The results obtained at that time were recently re-examined by a more exact method that permitted graphic registration. This method consists essentially in pressing an angularly bent rod, which is rotatable on an axis, against the arches of the diaphragm with the aid of a weight, whereby the diaphragm's tonus and the weight counter-balance each other. Alterations in tonus then govern graphically registrable alterations in the position of the umbilicus which are transferred, correspondingly enlarged, to a kymographion.

The experiments were carried out on dogs, cats and rabbits. On dividing the splanchnic nerves the diaphragmatic cupola shifted upward owing to tonus diminution. This phenomenon was observed almost regularly except in isolated cases in which the tonus-producing function of the splanchnic nerves had manifestly been already considerably injured during their exposure. The same diminution of tonus was effected by applying 1% nicotin solution to the celiac ganglion. It was preceded by increased tonus persisting several seconds and by enlargement of respiratory excursions, presumably an expression of transient irritation by the poison. The result remained the same if division of the splanchnic nerves had been carried out previously, while splanchnotomy following previous nicotization of the celiac ganglion remained without effect. Where the central surface of the diaphragm was painted with adrenalin solution after splanchnotomy or nicotization of the celiac ganglion, a distinct increase in diaphragmatic tonus was often observed. Painting with cocain solution after adrenalin application rarely produced transiently increased tonus; as a rule the latter diminished from the commencement. For unknown reasons, ammonia inhalation induced tonus diminution, as had been already observed by Sihle. Vagotomy had no influence on the diaphragm's tonus. It appears that diaphragmatic tonus is manifestly conditioned partly by the splanchnic nerves, namely, sympathetically. Further researches showed the diaphragm to be by no means free from tonus after splanchnotomy.

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### Diaphragmatic Tonus. III.

*Ken Kuré, Tohei Hiramatsu, Kenji Takagi and Masao Konishi, Arch. f. d. ges. Physiol., Berlin, 194:577, June 12, 1922.*

In 1914 Kuré, Hiramatsu and Naito, on the strength of experiments on rabbits, dogs and cats, decided in favor of an exclusively vegetative innervation of diaphragmatic tonus, because division of the splanchnic nerves, or nicotization of the celiac ganglion, induces distinct diminution of tonus. The new investigations compel a certain modification of this view. In order to obtain still clearer results the operations were now performed on apes, which possess a relatively large thoracic cavity; the diaphragm's position was determined by roentgenograms. The operations embraced evulsion of the phrenic nerve, division of the anterior roots, extirpation of the cervical sympathetic with its ganglia and eradication of the sympathetic fibers running to the abdominal surface of the diaphragm. Extirpation of the left celiac ganglion and of the left splanchnic nerve produced left-sided elevation of the diaphragm, which became indistinct a few weeks later, although individual differences were found. Therefore, relaxation was

not produced in spite of diminished tonus. Extirpation of the left abdominal sympathetic and evulsion of the left phrenic nerve abolished the tonus of the diaphragm's left side completely, it being pulled upward by the negative intrathoracic pressure. Evulsion of the phrenic nerve alone caused extreme diminution of tonus, which showed strong individual differences; in course of time elevation of the diaphragm lessened. Extirpation of the cervical sympathetic, i. e. exclusion of all sympathetic fibers running with the phrenic, causes no considerable relaxation. Division of the motor cervical roots induces not particularly extreme and persistent tonus diminution. When evulsion of the phrenic nerve was performed after division of the roots, tonus diminished considerably. Accordingly, it is obvious that exclusion of tonus necessitates simultaneous division of the spinal and sympathetic fibers. Simultaneous extirpation of the cervical and abdominal sympathetic increases tonus transiently, relaxation soon following. Combined division of the abdominal sympathetic and of the spinal roots effects greater tonus diminution than division of the latter alone. Consequently, diaphragmatic tonus is maintained simultaneously by sympathetic and spinal fibers. The authors assume that the sympathetic induces a nonmotor plastic tonus, the spinal roots one of a motor character, which increases during inspiration.

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**Localization of the Cortical Gustatory Center.**

*Walter Boernstein, Deutsch. Ztschr. f. Nervenhlk., Leipsic, 74:259, May, 1922.*

The opinion held by many authorities that the cortical centers for taste and smell are identical is improbable for anatomic as well as physiologic reasons. The taste center is probably localized in the operculum (Bechterew); in lesions of that region, disturbances of taste are observed on the contralateral side of the tongue.

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**The Physiology of Automatic Cord Reflexes in Man.**

*G. Marinesco, A. Radovici and V. Răscanu, J. de physiol. et de path. gén., Paris, 20:226, No. 2, 1922.*

The authors have examined reflexes present in cases of hemiplegia, paraplegia and tetraplegia. The latent period, summation phenomena and entire graphic tracing have been carefully analyzed. The 4 variables present in summation, namely, intensity, duration, number, and frequency of the stimuli, have not received sufficient attention. Intensity has been the factor principally studied, especially in cutaneous reflexes. Nevertheless, all 4 components are present whether stimuli be mechanical, chemical or electrical.

In the tests here discussed, the stimulus consisted of induction shocks applied to the skin. The latent period proves to be practically identical in tendinous and cutaneous reflexes and automatic action in the cord, but varies greatly in the several reflexes on account of variations in the length of the path traversed by the impulses. The summation phenomenon is essential in the functioning of nervous centers. The



2 following laws are very important: (1) The threshold-excitation intensity diminishes inversely with the frequency of the stimuli until a certain rate is reached, above which the intensity remains constant. (2) The number of stimuli which may act cumulatively diminishes directly with the frequency. Summation, present in automatism of the cord, is absent in tendinous and cutaneous reflexes. No method is known for producing summation in the reflexes of the skin and tendons, since a single mechanical stimulus, if of sufficient intensity, produces the reflex movement. The latent period and summation increase as reflexes are repeated. After 2 or 3 repetitions, even very strong, frequent and numerous stimuli cannot produce the reflex movement unless preceded by 15 to 20 minutes of rest. This fact is probably due to insufficient oxygen in the nerve center. Disturbances of the circulation and retarded gaseous exchanges in the nerve centers were especially present in the tetraplegic case. The increase in summation and the latent period may also be explained by a disturbance of the dynamogenic function of the cord centers resulting from lesions of the connections between cord and brain. In this theory, the refractory period of the cord neurons, becoming more prolonged after the occurrence of each motor reaction, necessarily increases the summation and latent period. Tracings of the reflexes and tabulations of the experimental conditions and results are given.

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**The Nerve Fiber Constitution of Peripheral Nerves and of Nerve Roots.**

*J. N. Langley, J. Physiol., London, 56:382, July 21, 1922.*

In the author's study of the constitution of nerves and nerve roots he has confined his observations to nerves treated with osmic acid, since this treatment gives decisive results on the questions Langley was interested in, particularly whether nonmyelinated fibers are present in small or large numbers in the posterior roots. The animals used, cats principally, were bled to death while chloroformed, and then the nerves to be studied were put through a definite histologic staining routine. The author found that the cutaneous nerves contain many nonmyelinated fibers, the nerves to skeletal muscle contain few. All anterior roots of the spinal nerves are distinguished from the posterior roots by containing a relatively large proportion of fibers  $13\mu$  and more in diameter, and a relatively small number of fibers of about  $7.5$  to  $11\mu$ . These differences were found to be most distinct in the lower cervical and lower lumbar regions. Very few nonmyelinated fibers and probably none enter the spinal cord in the posterior roots, the author believes. A large factor in determining the size of nerve fibers is the nature of the tissue with which they are connected.

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**Alterations of Myelinated Nerve Fibers Produced by Anesthetics and Various Nerve Poisons.**

*L. Lapicque and R. Legendre, J. de physiol. et de path. gén., Paris, 20:163, No. 2, 1922.*

The authors report results obtained in and after 1914. The tests were made in frogs. The spinal cord is destroyed and the tibial and

peroneal nerves uncovered. The transparent sheaths are especially favorable for study. Either nerve is dissected free from the surrounding tissues, which are kept moist, with fine bone points. When the nerve is freed to the knee and foot, the limb is gently sectioned, the origin and insertion of the nerve remaining intact. The preparation is mounted in cork in a moist chamber, and various solutions may be introduced by the suction obtained by blotting or filter paper.

The substances examined were cocain hydrochlorate, in 1, 2, and 3% solutions in normal saline; 1 and 2% novocain; chloroform, 1 part saturated water solution mixed with 9 parts normal saline; ether; 1 and 2% chloral; 0.7% solution chloralose; 1% morphin hydrochlorate; 1% scopolamin hydrochlorate; 1% strychnin sulphate; sodium oxalate; 3:1000 solanin hydrochlorate; curare; and general anesthesia with chloroform and ether.

The electric changes correspond with the morphologic. Progressive diminution of the chronaxia and rise of the rheobase extending to complete loss of excitability are accompanied by swelling of the myelin sheath sufficient to form protuberances occupying the entire axis cylinder. The effects of chloroform and ether are like those of cocain and novocain, notwithstanding the differences in the composition of these substances. The swelling myelin advances inward in degrees varying with the substance employed. When the lumps or protuberances are well marked, the axis cylinder is so much compressed that it almost disappears. The protuberances are not formed by folding of the sheath or external wall and are quite homogeneous. Photographic plates are given.

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**Double Tonic and Trophic Innervation of Voluntary Muscles. Reinforcement of Sympathetic Tonus and Tissue Reflexes.**

*Ken Kure, Tetsushiro Shinosaki, Michio Kishimoto, Michisaburo Sato, Nobuo Hoshino and Yoshinobu Tsukiji, Ztschr. f. d. ges. exper. Med., Berlin, 28:244, June 7, 1922.*

The authors performed animal experiments: (1) Removal of the left ventrolateral sympathetic in 24 dogs and 6 cats (extirpation of 9-10 ganglia). (2) Destruction of the central motor portion of the cerebral cortex through introduction of a long needle into the temporal fossa (in 5 monkeys and 24 dogs). (3) Initial operation as in Experiment 2, followed by the operation described in Experiment 1 (in 4 dogs and 2 monkeys). (4) Injections of adrenalin (*a*) in normal animals, in small doses—not exceeding 0.5 c.c. of the 1:1000 solution; and (*b*) in animals who had undergone the operation described in Experiment 1. (5) Determination of the exact creatinin content of various muscles in 6 rabbits, 15 dogs, 5 monkeys and 7 human cadavers.

Clinical observations were made along the same lines: (1) On the result of determinations of creatin content per kilo of body weight (creatinin quotient), both in healthy subjects and in individuals affected with various nervous conditions. (2) On the result of injections of adrenalin in patients suffering from lesions of the pyramidal tract. (3) On the effect of injections of adrenalin in individuals with in-

creased reflexes without lesions of the pyramidal tract, as in neurasthenia and hysterics, in convalescents from severe infectious diseases—thyroid, pleurisy—and in individuals with chronic rheumatism. (4) On the result of injections of adrenalin in individuals exhibiting diminished or absent tendon reflexes—cases of normal muscular atrophy, progressive muscular dystrophy, Addison's disease, beriberi, Weil's disease, etc. (5) Effects of adrenalin injections on the creatinin content of 24 hours' urine.

Conclusions: Total extirpation of the sympathetic results in lowering of sympatheticotonus and corresponds to a lowering of the creatin content in the muscles affected. Destruction of the motor area of the cerebral cortex results in increase of sympatheticotonus in the paralyzed extremities, the motor tonus being retained unchanged. Even in the absence of sympathetic tonus the centers in the spinal cord seem able—and that even after isolation from higher centers—to develop a compensatory, increased tonus. The heightened sympathetic tonus results in intensification of the patellar reflex. Diminution of sympatheticotonus causes diminution or total cessation of reflexes. As voluntary muscles possess a double innervation, through cerebrospinal and sympathetic fibers, each of these is capable of compensatory increase in tonicity during impairment of the other. The muscles concerned with respiration, the muscles of the back and of the pelvis contain numerous sympathetic fibers; the small muscles of the hand and the gastrocnemius contain very few. Even in man, lesion of the pyramidal tract results in increase of sympatheticotonus, which latter runs parallel with increase in the creatinin content of the urine. Adrenalin injections, by increasing the sympathetic tonus, result in increased creatinin output in the urine. Patellar and ankle clonus may be caused, even in the absence of lesion of the pyramidal tract, by increasing sympathetic tonus. Genuine and pseudoclonus are essentially identical. Every increase in irritability obtained after isolation from higher centers is caused by an increase in sympatheticotonus. The lax paralysis following complete transverse section of the spinal cord may thus be explained as due to absence of reinforcement of motor tonus. In the neurogenic dystrophies it is mostly the hand and foot muscles which are affected, whereas in progressive muscular dystrophy the shoulder girdle and muscles of the back are most frequently involved. The authors advance the following explanation therefor: In cases of lesion of the motor fibers, the sympathetic innervation remains intact. Thus the sympathetic tonus of muscles, particularly of those containing very many sympathetic fibers, is still at work, and it is only the small muscles, i. e. those containing very few sympathetic fibers, that undergo atrophy. In progressive muscular dystrophy, due to atrophy of the sympathetic fibers as well, there is greater atrophy of voluntary muscles.

As to parasympathetic innervation of striped muscles, the authors have effected some experiments on the latter by means of atropin and pilocarpin injections. They were able to show that there really exists an additional, parasympathetic, innervation of striped muscles; but this appears to exert a practically negligible influence on maintaining muscle tonus as compared with the sympathetic innervation. Stimulation of parasympathetic nerves results in fibrillary contractions and increase in tendon reflexes, as well as in ankle clonus, especially during anesthesia.

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**The Sympathetic Innervation of the Skin of the Toad.**

*K. Uyeno, J. Physiol., London, 56:359, July 21, 1922.*

The object of this work was to reinvestigate the origin of the sympathetic fibers supplying the skin glands of the toad. The author used toads weighing from 25 to 50 gm. and injected subcutaneously into their dorsal lymph-sac 0.2 to 0.5 c.c. 25% urethane. The cerebral hemispheres and a part of the midbrain were destroyed and the spinal cord exposed. The dura mater was cut through, the eighth to the tenth posterior roots of both sides and the cauda equina were tied separately and cut peripherally of the ligatures. Lifting the ligatures all the remaining spinal roots, both anterior and posterior, were cut at the nearest point to the cord and the spinal cord was removed. The roots floating in the blood and cerebrospinal fluid were tied with thin silk. The fine anterior and posterior roots of the third to the sixth nerves were generally tied and stimulated together. Experiments were made on 12 toads, and as a rule all the spinal roots except the first were stimulated. The author's results show that the second to the seventh nerves constantly contain secretory fibers, but the eighth does not always contain them. The ninth nerve has no secretory fibers. The overlapping of the areas of skin supplied by the successive nerves is great, the author found. Any given portion of the skin of the back is normally innervated by three spinal nerves.

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**The All or Nothing Response of Sensory Nerve Fibers.**

*E. D. Adrian and Alexander Forbes, J. Physiol., London, 56:301, July 21, 1922.*

This research was undertaken to determine whether the all or nothing relation held good for afferent as well as for efferent fibers, and incidentally to investigate the relation in mammalian nerves, since it is in mammalian preparations that the most interesting questions in this connection arise. Employing a frog's sciatic gastrocnemius preparation set up in a special chamber (illustrated in the article) the authors studied the response to stimuli in a region of decrement and have indicated graphically the strength of stimulus required at different stages of narcosis. Concerning the relation between strength of stimulus and initial size of impulse in the early stage of narcosis, the authors believe a stimulus of the threshold strength sets up an impulse large enough to travel the maximum distance in the narcotized region without extinction, and a stimulus weaker than this sets up no impulse at all. Thus there must be a lower limit to the initial size of the impulse in the early stages of narcosis. The authors show diagrammatically the relation between the strength of stimulus and the initial size of the impulse set up in a region of decrement. The diagram shows that in the normal nerve no variation in the size of the impulse is possible. When there is a slight decrement in conduction through unit length, as in the early stages of narcosis, the threshold stimulus sets up an impulse slightly smaller than the normal and an increase in the stimulus will

increase the initial size of the impulse until it reaches an upper limit equal to that in the normal fiber. If the decrement in unit length is greater, the threshold stimulus sets up a smaller impulse and there is a greater possibility of gradation. From the data recorded diagrammatically the authors deduce that there can be very little grading in the initial size of the impulse unless the fiber is in such a state that the impulse suffers a considerable decrement in traveling through unit length.

To detect the presence of decrement in conduction in mammalian sensory fibers, the authors used two methods, employing the internal saphenous of a cat in each case. The first method consisted in measuring the size of the electric response called up by an impulse which had traveled (*a*) a short, and (*b*) a long distance from its point of origin. The second and more delicate method of detecting a decrement in conduction was to produce impulses of very small intensity by stimulating during the period of recovery from a previous impulse, and to see how far these could travel without extinction. Both methods show that in a mammalian sensory nerve the impulse undergoes at most a very slight decrement in conduction through unit length and often none that can be detected at all.

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**Studies in Fatigue. XI. The Effect of Intravenous Injection of Massive Doses of Adrenalin upon Skeletal Muscle at Rest and Undergoing Fatigue.**

*Charles M. Gruber, Am. J. Physiol., 61:475, Aug. 1, 1922.*

In the author's experiments cats, anesthetized and then tracheotomized, were used. Sherrington shielded electrodes were applied to both anterior tibial nerves. The tendons of both anterior tibial muscles were isolated, cut, and to each was fastened a linen ligature. The ligature was fastened to a writing lever. The blood pressure was recorded from the right carotid artery by means of a manometer. The stimulating current was a maximum break induction shock. The stimulating current for the nonfatigued muscle was also a maximum break induction shock from an inductorium interrupted at a constant speed by a mercury key. The secondary poles of this inductorium were connected to the shielded electrode on the left anterior tibial nerve. Through a cannula placed in the right external jugular vein the adrenalin was injected usually within 15 seconds. The concentration and quantity of the solutions injected were 1 ml. and 5 ml. 1:100,000; 5 ml. 1:10,000 and 5 ml. 1:1000. The blood pressure style, muscle levers and the time marker were placed in a vertical line on the kymograph surface. The rate of the drum was always slow and the muscle contractions were recorded close together, 36-220 contractions per minute for the fatigued muscle. The nonfatigued muscle was stimulated 3 times at intervals of 10 seconds and then allowed to rest for 1 minute. The heights of the 3 contractions were averaged to find the normal. Frogs of the species *Rana catesbiana* were also used. The adrenalin was injected through a cannula placed in the left brachial vein. The apparatus (except that that for recording blood pressure was omitted)



was the same as that used in the experiments on cats. A study of the tabulated and graphic data recorded in the article shows that adrenalin injected intravenously has the same influence upon non-fatigued as upon fatigued muscle. It lowers the threshold (increases irritability) and increases the height of muscular contractions. The increase in the height of contraction is dependent, within limits, upon the concentration of adrenalin in the circulating blood, the rate of stimulation and the condition of the animal. The author says that the effects of adrenalin are only slightly, if at all, due to changes in blood pressure or bettered circulation. It does not neutralize or destroy the fatigue products but increases the irritability of the muscle whether fatigued or resting.

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**The Recovery Heat Production in Muscle.**

*W. Hartree and A. V. Hill, J. Physiol., London, 56:367, July 21, 1922.*

The authors have previously observed that in isolated muscle, following a short stimulus, there is, in the presence of oxygen, a prolonged production of heat, which is considerably reduced in the absence of oxygen. This delayed heat production was held to be associated with the oxidative removal of lactic acid. The present paper records a reinvestigation of the recovery heat production, with every possible precaution taken to ensure accuracy and consistency, over as long a period as possible after the stimulus. The authors employed combined thermopile and muscle chamber, with a double sartorius preparation of *Rana temporaria*. They found that there is delayed production of heat after activity, both in the presence and in the absence of oxygen, though much larger in the former case. This heat production starts at a low level, rises to a maximum, and then falls slowly to zero, the whole process occupying about ten minutes at 20° C. and longer at lower temperatures. The effect of temperature shows that the velocity of the process is controlled by that of some chemical reaction. The shape of the curve, and the position of its maximum but not its total area, depend upon the extent of the initial breakdowns. The shapes of the curves (illustrated in the article) show (1) that the anaërobic and the oxidative processes are of different characters; (2) that the recovery process takes place in at least two stages, and (3) that its rate is governed by that of some unknown bimolecular chemical reaction. The mean value of the total oxidative recovery heat production the authors found to be 1.5 times the total initial heat production; the mean value of the total delayed heat, in as rigorous an absence of oxygen as it is possible to attain, the authors found to be 0.5 times the initial heat production; treatment with potassium cyanid somewhat diminishes, but does not abolish, this delayed anaërobic heat. The authors state that in the oxidative removal of lactic acid, from one-fifth to one-sixth of the lactic acid is burnt, the remainder being restored as glycogen. The total initial heat production is about 285 cal. per gm. of lactic acid set free. This corresponds to the heat evolved in the production of lactic acid from glycogen, and its neutralization chiefly by the alkaline protein buffers of the muscle.

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**The Action of Adrenalin on the Permeability of the Investing Sheath of Muscle-Fibers.**

*Hermann Lange, Ztschr. f. physiol. Chem., Berlin, 120:249, June 24, 1922.*

By following the elimination of phosphoric acid it was possible to show that the degree of permeability of the sarcolemma varies in accordance with the functional condition. As a rule increased permeability corresponds to increased function. The condition of permeability of the investing sheath must be of decisive importance in the relations of the cells to their surroundings, particularly as regards the escape of metabolic products from, and the entry of nutrient materials and diverse other substances into, the muscle. It may therefore reasonably be assumed that the higher animals possess a mechanism that regulates the permeability of the limiting membranes of the various organs, perhaps similar to that by which the blood supply of the individual organs can be regulated. This influence might be exercised by nervous impulses or by hormones.

The investigations were restricted to the skeletal muscle of the frog and to a definite endocrine substance, adrenalin, that is, to an influence on permeability by hormonal means. Chemical and biologic measurements of the permeability of the investing sheath of muscle-fibers agree in showing that adrenalin can diminish the permeability of the cellular limiting layer in the striated muscle of the frog. The following result was obtained (*a*) in a considerable number of experiments in which the escape of phosphoric acid from the muscle interior (adrenalin muscle) is constantly diminished, and (*b*) in an experimental series in which the retardation in the occurrence of paralysis in isotonic cane-sugar solution can be determined on a muscle previously treated with adrenalin as compared with a control muscle. The adrenalin rapidly tends to make the cells impermeable and this action persists a long time in the resting muscle even after removal of adrenalin from the surrounding liquid. This may also be produced by subcutaneous injection of adrenalin in the living frog. The characteristic adrenalin action on cellular investing layers is still observable in dilutions of 1:10,000,000. Under certain circumstances (in winter frogs kept some days in an ice chest) strong diminution of the threshold stimulus was observable under adrenalin action, but under the influence of strong stimuli the adrenalinized muscle shows far greater contraction than the control muscle. Obviously therefore the muscle contractility is increased simultaneously with the lowering of threshold irritability. Various known effects of adrenalin are attributed to its action of diminishing permeability.

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**The Heat Production and the Mechanism of the Veratrin Contraction.**

*W. Hartree and A. V. Hill, J. Physiol., London, 56:294, July 21, 1922.*

In the authors' experiments a pair of sartorius muscles of *Rana temporaria* was mounted on a thermopile, and subjected to a small initial tension, and the course of the heat production after a stimulus found

by analyzing the photographic curves of galvanometer deflection. Most of the experiments were made at 15° C., the muscle being in nitrogen which had been freed from oxygen by passing it through two bottles of alkaline pyrogallol. Heat production due to oxidative recovery was thus entirely eliminated. A suitable interval for the analysis was found to be 1 sec. during the first 20 sec. of the contraction. After that a 5 sec. interval could be used without loss of accuracy. The tension was recorded on a smoked drum by a tension lever, the contractions being practically isometric. After a few preliminary stimuli to determine in the normal muscle (*a*) the strength of the maximal stimulus (always a short tetanus of 0.03 sec.), and (*b*) the corresponding heat rate and tension curves, the veratrin solution was introduced into the chamber, and left in for 4 or 5 minutes, after which it was blown out by nitrogen. The strength of the veratrin, made up in Ringer's solution, was usually .002% or less. In order to record the relatively enormous heat production of the veratrin contraction, the deflection was reduced by the introduction of a resistance about 15 times that of the thermopile and galvanometer together, the sensitivity of the galvanometer itself being left unchanged. Control curves were made on the dead muscle. The authors remark that in the prolonged isometric contraction of a veratrinized muscle there is a prolonged evolution of heat, the rate of heat production being proportional throughout to the force maintained. The absolute value of the ratio (heat rate ÷ force × length) is the same as that found in the ordinary prolonged contraction set up by a tetanic stimulus. These facts show that the effect of veratrin cannot be ascribed to a slowing of relaxation, or of the chemical processes by which the acid which excites the mechanical response is removed from the site of its activity; it can only be supposed that it puts out of action, more or less completely, the regulating mechanism by which the duration and extent of the liberation of energy (and lactic acid) following a single shock, are limited and controlled.

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**The Cause of the Shortening of Dried Muscle-Fibers on Addition of Liquids.**

*Wolfgang Straube, Arch. f. d. ges. Physiol., Berlin, 194:574, May 17, 1922.*

An investigation was made of the shortening observed by Huerthle in muscles dried in the frozen state on the addition of a drop of Ringer's solution. Water alone effects intumescence but no contraction. Positive results were yielded by 0.01% sodium bicarbonate solution only, and no material influence of the concentration on the degree of shortening is concerned therein. The investigation of various acids showed the shortening effect to be due solely to carbon dioxid. The assumption that shortening is produced by lactic acid formed during the freezing of the muscles is therefore erroneous. Carbon dioxid produces contraction in the surviving muscle also. Accordingly carbon dioxid is probably of determining importance for the process of contraction in the living muscle.

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**Recent Results of Muscle Pharmacology.**

*Riesser, Klin. Wchnschr., Berlin, 1:1317, 1374, June 24, July 1, 1922.*

The movements of living skeletal muscles, connected with the central nervous system, are never purely tetanic in character, but are always the result of tetanus plus tonus. The coöperation of tetanic stimulations and the tonic condition, under regulation of the nervous system, is of special significance in the tonic condition of the skeletal muscles after metabolic processes. Smooth muscles remain in the state of contraction even without any increase of metabolism and without any oscillatory variations of the action current—apparently because of insufficient intensity of the counteracting processes. The different behavior of striated muscles is caused by the different intensity and rapidity of the processes of excitation corresponding to the decomposition and formation of the contractive substances and by the character of the reacting muscular elements. Pathologic permanent contractures of the striated muscles in general paralysis, Wilson's disease, catatonia, tetanic rigor, and hysteria have the following features in common with permanent contraction of smooth muscles: absence of phenomena of fatigue, of increased metabolism, of increased heat production, and especially of the oscillating action currents, which are characteristic of tetanic contraction. It must be admitted, however, that very weak action currents have been observed, so that there is only a quantitative difference between the pathologic permanent contractions and the ordinary tetanic contractions of the skeletal muscles. The former may be described as a tonic modification of tetany, in which the tonus is intensified while the tetanic excitation is diminished. This condition finds its explanation in the absolutely identical behavior of the muscles in Sherrington's decerebrate rigidity. The cause is to be sought in the removal of inhibitory influences exerted by the cerebrum on the mesencephalic centers controlling muscle tonus. The disappearance of the rigidity after severing the sensory muscle nerves proves that decerebrate rigidity is a reflex, excited and sustained by sensory stimulations from the muscles (proprioceptive reflex). Both the individual tonic contraction and the tonic modification of tetanus have the same causes and are subject to the coöperation of a nervous reflex regulation.

Normal and pathologic motor processes are excited by physicochemical alterations, but undoubtedly, in the latter, functional factors also play a part, as is suggested by the influence of nicotin and acetylcholin on skeletal muscles. The permanent contraction produced by these poisons, the so-called "excitation contracture," which is certainly not in the nature of tetanus, forms the closest approximation to permanent contraction of smooth muscles.

**URINARY SYSTEM**

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**Secretion by the Isolated Kidney.**

*E. B. Verney and E. H. Starling, J. Physiol., London, 56:353, July 21, 1922.*

In the authors' experiments 2 dogs were used, one supplying the kidney and the other being used for the preparation of the isolated

heart-lung. The first dog was given morphin, anesthetized with chloroform and ether and then bled to the extent of approximately 350 c.c. A heart-lung preparation was then made on the second dog under morphia and chloralose anesthesia. The blood obtained from the first dog was defibrinated and used for this preparation. Artificial respiration was maintained by means of a Meyer pump. It was found that the kidney of the first dog, when perfused with blood from the heart-lung preparation, was capable of secreting urine in considerable amounts. The rate of blood flow through this organ and the rate of secretion varied directly as the blood pressure in the renal artery. Normal saline, urea and sodium sulphate were found to exert a diuretic effect on the kidney perfused under these conditions, without any corresponding increase in the blood flow. The kidney was also found to be capable of concentrating urea and glucose and of retaining chlorid.

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**The Excretion of Chlorids and Bicarbonates by the Human Kidney.**

*H. W. Davies, J. B. S. Haldane and G. L. Peskett, J. Physiol., London, 56:269, July 21, 1922.*

The experiments here recorded were made to determine the relations between the various concentrations which are possible in the urine at the same time. All experiments but one were made on one of the authors. Chlorids were estimated by Volhard's method, bicarbonates with J. S. Haldane's blood-gas apparatus, phosphates with uranium acetate and cochineal, and urea by Krogh's or Marshall's method. In the tabulated results concentrations are expressed in terms of normality, or for phosphates in terms of molarity. Volumes are given in cubic centimeters, weights in grams. It was found that when strong solutions of NaCl were drunk, the urinary chlorid concentration rose rapidly to a value varying between 0.29 n. and 0.33 n., the value being independent of the volume excreted per hour, and only rising slightly when more salt was taken. The limit of 0.330 n. was only passed during extreme thirst, the highest value recorded being 0.338 n. Of 70 bicarbonate concentrations determined on the same subject, only one exceeded 0.330 n. Values higher than 0.320 n. were reached on several occasions. The maximum molecular concentrations of chlorid and bicarbonate are therefore practically identical. When chlorid and bicarbonate were taken together or successively both appeared in the urine in large amounts. Neither reached its maximum concentration, but the sum of the two reached a value which (expressed in normality) was equal to the maximum of either. If bicarbonate be given without chlorid the latter may almost disappear from the urine, the authors found. Simultaneous excretion of urea was found to be without effect on the kidney's capacity for concentrating chlorid and bicarbonate; but urea ingestion, though it may lower the chlorid concentration by promoting diuresis, considerably increases the output per hour.

The authors conclude that chlorids and bicarbonates must be concentrated by the same part of the kidneys, which is probably reabsorptive, urea and phosphates by a different one, which is excretory.



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**Studies of Urinary Acidity. I. Some Effects of Drinking Large Amounts of Orange Juice and Sour Milk.**

*N. R. Blatherwick and M. Louisa Long, J. Biol. Chem., 53:103, July, 1922.*

Two healthy young women volunteered as subjects for this study. One subject was given a uniform basal diet composed of baked potato, 260 gm.; whole milk, 440 gm.; graham crackers, 300 gm.; raw apple, 150 gm.; cheese, 25 gm.; butter, 45 gm.; egg, 65 gm. The diet of the other subject was similar with the exception that she ate no egg. After 4 days on this basal diet the effect of increasing amounts of strained orange juice was determined. The tabulated results show the effects on the urine of drinking large amounts of orange juice; a marked increase in the pH value (less acidity), an increased excretion of organic acids, and a marked decrease in the ammonia output. In the lactic acid experiments a basal diet of 2 liters of whole milk and 340 gm. of soda crackers was selected. This diet amply satisfies the ordinary requirements and is one which should theoretically yield a neutral urine. On the experimental days 2 liters of the lactic acid milk were substituted for the whole milk, when these effects on the urine were observed: (1) a marked decrease in pH (increased acidity); (2) a marked increase in the titratable acidity; (3) a marked increase in the phosphorus content; (4) a significant increase in the ammonia output; and (5) no change in the organic acidity.

**ENDOCRINE GLANDS**

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**The Effect of Lesions of the Hypophysis and of the Cerebrum on the Cutaneous Changes of Frogs.**

*L. Giusti and B. A. Houssay, Rev. Asoc. méd. argentina, Buenos Aires (Biol. Sect.), 35:42, Jan.-April, 1922.*

Extirpation of the hypophysis produced a dark bronze or black discoloration of the skin, appearing in 4 or 5 days in September, in 2 or 3 days in the hot months of January and February, and in 8-15 days during the cold period. The cutaneous discoloration became more accentuated and persisted for several months. It involved the ventral surface mainly. In some cases the mouth, paws or the ventral surface became ulcerated. The discoloration was due mainly to the accumulation of superficial horny layers in the skin, which did not slough off. The change was hyperkeratotic rather than pigmentary. The number of the cellular layers was normal, but the cells were infiltrated, and the horny layer thickened.

In one series of cases craniotomy or a cerebral lesion did not produce these changes. However, the lesions were in areas distant from the hypophysis. For this reason the experiment was repeated, the site of the lesion being adjacent to the hypophysis. The injury was produced with a red-hot needle. Darkening of the skin ensued. The cerebral zone capable of producing this change appears to be extremely limited, and includes the area immediately anterior and that immediately posterior to the hypophysis.

The experiments demonstrated the presence of a nervous zone

surrounding the hypophysis, disturbances of which produce cutaneous changes in frogs. The experimental administration of the gland extract, orally and subcutaneously, in the case of hypophysectomized frogs, demonstrated that the cause of the cutaneous changes was not glandular insufficiency.

All the hypophysectomized females evacuated large translucent gelatinous cylinders containing developed ovules in September, i. e. prematurely. The animals which had undergone craniotomy or injury to an area distant from the hypophysis did not present these changes. Apparently the hypophysis exerts a marked influence upon the genital system of the frog.

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**Experimental Contributions on the Internal Secretion of the Pituitary Body and of the Parathyroid Glands.**

*G. Izumi, Japan Med. World, Tokio, 2:199, July 15, 1922.*

In order to know the function of the endocrine glands, the author made a histologic study of the relations between the pituitary and parathyroid, the pituitary and thyroid, the thyroid and parathyroid, and the pituitary and gonads, with 49 cats and 127 rats. Experimentally the parathyroprivic rats and cats showed that the chromophil cells decreased remarkably in number and size in the pars anterior of the pituitary, while the chromophobe cells increased in number. After removal of the parathyroid, the pituitary body of the rat in almost every case became smaller, while that of the cat always enlarged 2-4 times normal size. The source of this enlargement is mainly proliferation of the cellular element of the pars intermedia. In the thyroprivic cats, enlargement of the pituitary was always seen, caused principally by proliferation of the pars anterior, partially through the hypertrophy of the peduncle. The source of the former is the extreme proliferation of basophil cells, while the latter has an increase of epithelial cells which accumulate much of the secretion in its acinus.

It was shown that the pituitary of castrated rats is larger than normal, due to the appearance of the castrate cells in the pars anterior. According to the ability of these cells to stain, it will be noted doubtless that these castrate cells are descending from the eosinophile cells of pituitary. The feeding of the parathyroprivic rats with phosphorus cod-liver oil and calcium lactate had no therapeutic influence on their opaque degenerating teeth. The total or partial removal of the thyroid or total castration had no clinical effect upon the course of tetany, which results with the enucleation of the parathyroid of the rats.

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**The Influence of Parathyroidectomy on the Skeleton of Animals Normally Nourished, and on Rickets and Osteomalacia Produced by Deficient Diet.**

*V. Korenchevsky, J. Path & Bacteriol., Edinburgh, 25:366, July, 1922.*

The author's experiments were conducted with a view to ascertaining whether the removal of the parathyroid glands in normal animals kept on a normal diet causes the appearance of rickets or osteomalacia

and whether the removal of these glands in rats produces an increase in the changes of the skeleton resulting from diets deficient in calcium, vitamin A, or in both factors simultaneously. He used 35 rats, from 21 of which the parathyroids were successfully removed. The remaining 14 served as controls. The procedure was similar to that employed in his first experiments of this nature. In each experiment the rats belonging to the same litter were kept on 4 different diets: normal, deficient in calcium, deficient in vitamin A, and deficient in both factors. Korenchevsky was unable to confirm the results of Erdheim on the rickets-producing effect of the removal of parathyroids; apparently parathyroidectomy produces no marked influence on the skeleton of rats kept on normal or rickets-producing diets. These experiments confirm the author's previous observations that (1) vitamin A has an important relation to the metabolism of calcium in the organism and particularly in the bones and to the etiology of rickets or osteomalacia; (2) the changes typical of rickets or osteomalacia occur most readily and most frequently in rats kept on a diet deficient in both vitamin A and calcium.

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**Influence of Glands with Internal Secretion on the Respiratory Exchange. IV. Effect of Suprarenal Insufficiency in Cats.**

*W. J. M. Scott, J. Exper. Med., 36:199, Aug. 1, 1922.*

In this report are recorded the changes in heat production observed in cats following varying degrees of suprarenal injury produced by partial extirpation, vessel ligation, freezing, and various combinations of these procedures. Cats were kept in the laboratory under uniform conditions of régime and diet for at least 3 weeks before determination of the respiratory exchange. The gaseous metabolism was measured, the room temperatures being kept relatively constant, and determinations were always made at least 15 hours after the last feeding. A sufficient number of them over a period of at least 2 weeks was obtained to determine the normal range for the individual cat under given conditions.

Three methods were used to cripple the suprarenal function: (1) partial excision; (2) ligation of blood vessels; and (3) freezing. Of these methods, partial excision was entirely unsatisfactory. Vein ligation gave good results in some cases but the collateral circulation was a dominant factor which could not be predicted or controlled. Freezing offered the most satisfactory means of controlling suprarenal injury. In some cats both glands were frozen by the ethyl chlorid spray, though more frequently the left was frozen and the right excised. The duration of the freezing varied from 15 to 45 seconds, depending on the degree of injury desired. For skin sterilization an alcoholic picric acid solution was used instead of iodine which would tend to confuse studies of thyroid function.

Two types of control experiments were made: (1) freezing around the mobilized suprarenals; and (2) excision of one suprarenal gland. Thirty-five experiments were conducted on 24 cats in which the respiratory exchange was followed before and after operation by freezing, 10; ligation, 17; partial removal, 6; operative trauma, 2. The types of reaction to subtotal suprarenal insufficiency as observed in these cats may be roughly classified into 3 groups.

Group 1. In this group the animals survive indefinitely and there is no increase in heat production of over 10% ; 8, or 30% of the experiments following freezing or ligation, presented this type of response. The suprarenals at autopsy or at subsequent operation showed large areas of uninjured cortex, and the medulla appeared quite normal.

Group 2. This group includes those cats whose heat production following operation increased at least 10% above the highest preoperative figure ; 12, or 44% of the freezing or ligation experiments, showed this type of reaction. The increase varied from 18 to 44% above the preoperative average and from 10 to 30% above the highest preoperative figure. With 1 exception the rise in basal metabolism lasted 9-38 days before again reaching the preoperative level. The increase in heat production was absolute as well as relative and in every case the cats survived indefinitely. Following this phase of increased heat production a slight depression averaging 10% below the normal usually occurs, lasting 1-4 weeks. That this may be partly due to exhaustion of the thyroid is suggested by 2 facts: (1) Potassium iodid given in 2 cases during this period of depression was followed by a prompt return to normal. (2) In several instances the thyroid was found 30 days after saturation with KI to be markedly hyperplastic in cats which had shown an increased basal metabolism after suprarenal crippling. This work shows that partial suprarenal cortex insufficiencies produced experimentally are transitory and that compensation takes place rapidly or the animal dies. The clinical syndrome of suprarenal insufficiency in cats bears many points of resemblance to Graves' disease ; the most prominent phenomenon in each is increased heat production. Each has a phase of asthenia and exhaustion, with evidence of severe cardiac damage ; diarrhea, and nutritional and weight changes are common to each. Hyperplasia of the thyroid is produced in each and is characteristic of neither.

Group 3. In this group the metabolism decreases slowly or rapidly until death. Seven, or 26% of the animals, reacted in this way after freezing or ligation. The decrease in metabolism averages 25%. Histologic examination of the suprarenals showed in each instance marked injury to the cortex. At autopsy the heart is somewhat dilated and the musculature is flabby, accounting for the cardiac weakness manifested by animals with fatal suprarenal insufficiency. Controls: In the 2 cats in which both glands were mobilized and the tissues about the glands frozen, the heat production showed no increase. The 5 animals in which 1 suprarenal was removed were likewise unaffected. That these animals could show the typical rise in basal metabolism was demonstrated in 3 of these 5 cats by either previous or subsequent operation.

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**The Function of the Suprarenals. New Researches on the Vasomotor Action of the Great Sympathetic Nerve in Certain Mammals (Ungulates and Rodents).**

*E. Gley and A. Quinquaud, J. de physiol. et de path. gén., Paris, 20:193, No. 2, 1922.*

The authors examined the vasomotor effect produced by stimulating the splanchnic nerve. In the cat and dog the reaction occurs in 2

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stages. There are at first a rise and fall, then a second and very considerable rise. In a series of rabbits, the effect occurred only in 1 stage. The experiments have been extended to other rabbits, an Argentine rodent, and to goats, horses, mules and cows.

The original results obtained in rabbits prove to have been incomplete. The 2 stage reaction is present in all the animals examined, including rabbits. It simply varies with the species. The variations indicate that the second stage of the reaction does not always depend upon secretion of adrenalin, for were the latter constantly produced by splanchnic stimulation it should produce a constant effect. Blood pressure tracings are given.

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### **The Relation of the Adrenals to Muscular Activity.**

*Frank A. Hartman, Endocrinology, 6:511, July, 1922.*

The most characteristic symptom of adrenal insufficiency is muscular asthenia. After the discovery of epinephrin it was shown that this substance could benefit fatigued muscle. This suggested the possible rôle of the adrenals in muscular exercise. The influence of exercise in 50 cats by means of a treadmill, most of them for a few weeks and a smaller number for considerably more than a year, was studied. The results point to a very definite relation between epinephrin output and muscular response. The denervated pupil was used as a test for epinephrin. That epinephrin is responsible for dilatation of the denervated pupil during exercise has been shown by denervation of the adrenals in animals which gave the reaction, after which dilatation was abolished. It was proven that dilatation is not due to central nervous influence, by removal of the ciliary ganglion as well as the superior cervical ganglion.

In the 5 cats in which this operation was performed exercise in the treadmill easily elicited dilatation of the denervated pupil. Abolition of dilatation of the pupil following complete adrenal ablation in cats with the superior cervical ganglion removed and the response of a completely denervated iris with adrenals intact, are conclusive evidence that the dilatation during exercise must be due to something from the adrenals. Epinephrin, being the only substance in the adrenals known to possess this power, must be responsible for the dilatation of a denervated pupil from exercise.

In normal animals, except in rare instances, there is an increase in the output of epinephrin accompanying exercise. This increase is greater, the more vigorous and the more prolonged the exercise. The increased output of epinephrin persists for some time after the exercise ceases, the duration of the increase depending to some extent upon the amount of work performed. Adrenalin injections (intramuscularly) improve the output of work in many normal cats and in cats with epinephrin deficiency. An animal can go farther and travel faster when there is an increase in the epinephrin output during exercise. From the study of 4 cats, 3 of which had previously been seized by convulsions, it was found that epinephrin hastened the onset of convulsions due to exercise.



1b. BIOLOGIC AND ORGANIC CHEMISTRY

(1b—74)

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On the Influence of Changes of Concentration of the Resp. OH' Ions on the Life of the Tissue Cells of Vertebrates. I. The Influence of Temporary Changes of Reaction of the Medium.

*A. A. Krontovski and V. V. Radzimovska, J. Physiol., London, 56: 275, July 21, 1922.*

The object of the authors' experiments was to determine the concentration of hydrogen and hydroxyl ions compatible with life. For the observations the spleen of the rabbit was selected because its cultivation outside the organism gives very good and uniform results. As acid solutions the authors employed lactic acid buffer and acetic acid buffer; as alkaline solutions the borate mixture of Sorensen and the ammoniacal mixture of Michaelis. Cultures of small pieces of the spleen in buffered mixtures were made outside the body. The experimental pieces were placed for half an hour in a mixture with a given H-ion concentration. The control pieces were left for the same time in Ringer's fluid. Then all were placed in a mixture of serum and plasma. It was found that the maximum concentration of hydrogen ions in lactic acid mixtures which left the cells still alive and capable of growth was pH 4.04, with acetic acid mixtures it was pH 5.33 (in one case 5.05). This difference in action shows that the influence of the mixtures depends, not only on the H-ion concentration, but also upon other factors. The minimal concentration of hydrogen ions compatible with the life of the cells was pH 10.28. The results show that the lymphocytes, reticular cells and fibroblasts of the spleen retain life when the reaction of the surrounding medium undergoes considerable change either to the acid or to the alkaline side—a degree of change which does not occur in the body either in physiologic or pathologic conditions.

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Further Studies on the Hydrogen-Ion Concentration of Human Sweat.

*G. A. Talbert, Am. J. Physiol., 61:493, Aug. 1, 1922.*

The experiments herewith recorded were made upon naked subjects. The sweat produced by work was induced by the use of a stationary bicycle in a room at a temperature 25°-30° C. The heat sweat was produced while the subject was enclosed, except his head, in an ordinary sweat cabinet. The average temperature inside the cabinet was about 40° C. The author followed the same method of acidity determination as reported in his first paper. The skin was always well cleansed with soap followed by distilled water, ether and alcohol applied with dental napkins. It was found that when sweat is secreted under the same environmental conditions, except temperature, the work and heat sweat gave the same hydrogen ions. The sweat collected from the skin covered with a rubber jacket yielded higher hydrogen ions because there was not quite the freedom for the escape of the volatile organic acids.

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**Cell Penetration by Acids. V. Note on the Estimation of Permeability Changes.**

*W. J. Crozier, J. Gen. Physiol., 4:723, July 20, 1922.*

The author has studied the penetration of acid into mantle tissue of *Chromodoris zebra*, the acid chosen being usually dichloroacetic. The effect (on the rate of acid penetration) was observed as regards tension, faradic stimulation and anesthetics (ether, ethyl alcohol, chloroform and magnesium sulphate). The author found that the penetration of acid into mantle tissue of *Chromodoris zebra* is accelerated after local faradic stimulation, and is retarded by brief treatment with anesthetic solutions. The spontaneous outward diffusion of intracellular pigment is an inadequate criterion of "permeability." Such a method of observation ignores the fact that the pigment concerned may be held in the cell, not by the state of the cell surface primarily, but by the relation of the pigment, especially when in the form of droplets, to the cytosome as a whole. Outward diffusion of pigment and penetration of acid are both facilitated when the tissue is put under artificial tension.

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**On the Influence of Aggregates on the Membrane Potentials and the Osmotic Pressure of Protein Solutions.**

*Jacques Loeb, J. Gen. Physiol., 4:769, July 20, 1922.*

Loeb studied the influence of substitution of powdered for dissolved gelatin in osmotic pressure and differential pressure. It is shown that when part of the gelatin in a solution of gelatin chlorid is replaced by particles of powdered gelatin (without change of pH) the osmotic pressure of the solution is lowered the more the more dissolved gelatin is replaced by powdered gelatin. It is therefore obvious that the powdered particles of gelatin do not participate in the osmotic pressure of the solution in spite of the fact that they participate in the establishment of the Donnan equilibrium and in the membrane potentials.

This paradoxical phenomenon finds its explanation in the fact that as a consequence of the participation of each particle in the Donnan equilibrium, a special osmotic pressure is set up in each individual particle of powdered gelatin which leads to a swelling of that particle, and this osmotic pressure is measured by the increase in the cohesion pressure of the osmotic pressure of the powdered particles required to balance the osmotic pressure inside each particle. In a mixture of protein in solution and powdered protein there are therefore 2 kinds of osmotic pressure, the hydrostatic pressure of the protein which is in true solution, and the cohesion pressure of the aggregates. Since only the former is noticeable in the hydrostatic pressure which serves as a measure of the osmotic pressure of a solution, it is clear why the osmotic pressure of a protein solution must be diminished when part of the protein in true solution is replaced by aggregates.

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**Studies in the Physical Chemistry of the Proteins. I. The Solubility of Certain Proteins at Their Iso-Electric Points.**

*Edwin Joseph Cohn, J. Gen. Physiol., 4:697, July 20, 1922.*

In the author's experiments 2 proteins of the globulin type, serum globulin, tuberin and the protein of milk, casein, were each purified as far as possible from other proteins, from multivalent anions and cations, and from all but the last trace of electrolytes, by special methods adapted to the nature of each. They were first prepared either as ammonium or as sodium compounds. Analyses were then made of the amount of ammonia or of sodium in these compounds, and the amount of hydrochloric acid required to neutralize the base and precipitate the protein at its isoelectric point was calculated. All 3 proteins were found to be only very slightly soluble in water in the pure uncombined state. The solubility of each was accurately measured at  $25.0^{\circ} \pm 0.1^{\circ}$  C. The most probable solubility of the pseudoglobulin of serum was found to be 0.07 gm. in 1 liter; of tuberin 0.1 gm. and of casein 0.11 gm. Each protein investigated dissolved in water to a constant and characteristic extent when the amount of protein precipitate with which the solution was in heterogeneous equilibrium was varied within wide limits. The solubility of a pure protein is proposed by the author as a fundamental physicochemical constant, which may be used in identifying and in classifying proteins. The concentration of protein dissolved must be the sum of the concentration of the undissociated protein molecule which is in heterogeneous equilibrium with the protein precipitate, and of the concentration of the dissociated protein ions. The dissociated ions of the dissolved protein give a pH to water that is also characteristic of each protein.

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**The Mechanism by Which Trivalent and Tetravalent Ions Produce an Electric Charge on Iso-Electric Protein.**

*Jacques Loeb, J. Gen. Physiol., 4:741, July 20, 1922.*

The author's previously reported experiments on anomalous osmosis suggested that salts with trivalent cations, e. g.  $\text{LaCl}_3$ , caused iso-electric gelatin to be positively charged, and salts with tetravalent anions, e. g.  $\text{Na}_4\text{Fe}(\text{CN})_6$ , caused iso-electric gelatin to be negatively charged. In this paper is published direct measurements of the differential pressure between gels of iso-electric gelatin and an aqueous solution as well as between solutions of iso-electric gelatin in a collodion bag and an aqueous solution, which show that the author's suggestion was correct. The experiments on anomalous osmosis suggested that salts like  $\text{MgCl}_2$ ,  $\text{CaCl}_2$ ,  $\text{NaCl}$ ,  $\text{LiCl}$  or  $\text{Na}_2\text{SO}_4$  produce no charge on iso-electric gelatin and it is shown in this paper that direct measurements of the P.D. support this suggestion.

Concerning the nature of the mechanism by which trivalent and tetravalent ions cause the charge of iso-electric proteins, the author shows that salts with such ions act on iso-electric gelatin in a way similar to that in which acids or alkalies act, inasmuch as in low concentrations the positive charge of iso-electric gelatin increases with the concentration of the  $\text{LaCl}_3$  solution until a maximum is reached at a concentra-

tion of  $\text{LaCl}_3$  of about M/8000; from then on a further increase in the concentration of  $\text{LaCl}_3$  diminishes the charge again. This is also true for the action of  $\text{Na}_4\text{Fe}(\text{CN})_6$  and from this it is inferred that the charge of the iso-electric gelatin under the influence of  $\text{LaCl}_3$  and  $\text{Na}_4\text{Fe}(\text{CN})_6$  at the iso-electric point is due to an ionization of the iso-electric protein by the trivalent or tetravalent ions. Solutions of  $\text{LaCl}_3$  and  $\text{Na}_4\text{Fe}(\text{CN})_6$  influence the osmotic pressure of solutions of iso-electric gelatin in a similar way as they influence the P.D. inasmuch as in lower concentrations they raise the osmotic pressure of the gelatin solution until a maximum is reached at a concentration of about M/2048  $\text{LaCl}_3$  and M/4096  $\text{Na}_4\text{Fe}(\text{CN})_6$ . A further increase of the concentration of the salt depresses the osmotic pressure again.  $\text{NaCl}$ ,  $\text{LiCl}$ ,  $\text{MgCl}_2$ ,  $\text{CaCl}_2$ , and  $\text{Na}_2\text{SO}_4$  do not act in this way.

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**Ionizing Influence of Salts with Trivalent and Tetravalent Ions on Crystalline Egg Albumin at the Iso-Electric Point.**

*Jacques Loeb, J. Gen. Physiol., 4:759, July 20, 1922.*

The fact that ionization of protein prevents heat coagulation of albumin can be used to determine whether other electrolytes than acids or alkalies are able to produce ionization of isoelectric egg albumin. If other ions, like La, Ca, Na,  $\text{SO}_4$ , have such an effect on aqueous solutions of isoelectric albumin, it should show itself in the prevention of heat coagulation and in the optical appearance of the albumin solution after heating. The author's experimental procedure was as follows: 7 c.c. of water of pH 4.8 (this pH being the isoelectric point of crystalline egg albumin) were added to 2 c.c. of 1 per cent solution of isoelectric crystalline egg albumin (pH 4.8) and then 1 c.c. of a salt solution containing different salts of different concentration, but always of pH 4.8, was added. The test-tubes containing the 10 c.c. of the mixtures were put into boiling water until the liquid in them reached a temperature of 90 degrees C. and then the test-tubes were taken out of the water bath and allowed to cool at room temperature. The results show that salts with trivalent or tetravalent ions, e.g.  $\text{LaCl}_3$  or  $\text{Na}_4\text{Fe}(\text{CN})_6$ , are also able to prevent the heat coagulation of albumin at the isoelectric point (i.e. pH 4.8) while salts with a divalent ion, e.g.  $\text{CaCl}_2$ ,  $\text{BaCl}_2$ ,  $\text{Na}_2\text{SO}_4$ , or salts like  $\text{NaCl}$ , have no such effect.

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**The Physiology of Creatin.**

*Otto Riesser, Ztschr. f. physiol. Chem., Berlin, 120:189, June 24, 1922.*

A mixture of rabbits' skeletal muscles has a remarkably constant creatin content. Thus, in numerous examinations, an average value of 0.450%, with slight variations, was found. On the other hand, the creatin content of the individual muscles is by no means constant, almost every muscle possessing its own creatin value. The present researches show clearly that, as a rule, the more rapid the contraction of a muscle, the greater its creatin content. The creatin content of

different kinds of muscles is inversely proportional to its relative sarcoplasm content and is directly proportional to the content of striated structures. Hence quick and slow muscles should be distinguishable by their creatin content. Further investigations dealt with the distribution of creatin and lactacidogen. The behavior of the creatin and lactacidogen content of various kinds of muscles is identical. No parallelism exists, however, in the behavior of the two substances in alterations of the muscular condition induced by dissimilar factors. Creatin content in particular is not increased either by heat or in rigor mortis, so that the creatin content of dead muscle may serve as a measure of the intravital content. Kahn's statement that the creatin content of a prehensile frog's "tonically" shortened foreleg muscles is less than normal is not justifiable. The creatin content of the foreleg muscles (slow) is always considerably less than that of the hindlegs and in this respect no difference exists between prehensile and non-prehensile frogs.

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#### **The Origin of Creatin and Creatinin.**

*H. Steudel and R. Freise, Ztschr. f. physiol. Chem., Berlin, 120:244, June 24, 1922.*

The formation of creatin and creatinin in the process of metabolism is related to the nitrogen metabolism of the so-called basal metabolism because elimination of these substances proceeds uniformly and is independent of the protein intake. The guanidin-yielding complexes of protein substances, particularly arginin, have frequently been regarded as the mother substances, though no positive proof has been furnished. On the other hand, being an imidazol derivative, creatin stands in a certain relationship to the purin bodies, which likewise contain an imidazol nucleus and the pyrimidin nucleus of which can be readily decomposed to an imidazol derivative by oxidation, as, for instance, uric acid to parabanic acid. Finally, creatinin is close to histidin which is imidazolyalanin.

The behavior of yeast-nucleic acid and histidin was examined in regard to creatinin formation in female dogs fed on creatinin-free diet before the experiment. It was shown in the experiments that no connection exists between yeast-nucleic acid and histidin and their individual split products, on the one hand, and creatin and creatinin, on the other. Nevertheless a considerable alteration in metabolism seems to take place after intravenous injection, as sugar appeared in the urine in one case.

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#### **The Combination of Gelatin with Hydrochloric Acid.**

*David I. Hitchcock, J. Gen. Physiol., 4:733, July 20, 1922.*

Hitchcock checked up some work of Lloyd and Mayes who had obtained a curve to represent the amount of HCl combined with 1 gm. of gelatin. The amount of HCl combined with a given weight of gelatin was determined by hydrogen electrode measurements in 1%, 2.5% and 5% solutions of gelatin in HCl of various concentrations, by correcting for the amount of HCl necessary to give the same pH to an



equal volume of water without protein. The curve so obtained indicated that the amount of HCl combined with 1 gm. of gelatin is constant between pH 1 and 2, being about 0.00092 millimoles.

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**On Protamins.**

*R. E. Gross, Ztschr. f. physiol. Chem., Berlin, 120:167, June 24, 1922.*

The successful preparation of the split products of protamins—the protons—by hydrolysis with dilute mineral acids as well as by suitable pepsin digestion and pepsin action is important in relation to the constitution of the protamins. From the protons the amino-acids were derived by further hydrolysis. In nearly all protamins the molecular proportion of diamino-acids to monamino-acids is as 2:1. Researches were undertaken in order to gain further insight into the structure of the clupein molecule. The proportion of total nitrogen to free amino-nitrogen was determined by Kjeldahl's method and Sørensen's formol titration and later, in order to save material, by Van Slyke's micro-method. For the Kjeldahl estimations 0.05 n. solutions and for formol titration 0.1 n. sodium hydroxid were employed. With Van Slyke's method, however, the samples were shaken from time to time. All analyses were carried out in duplicate. The experiments showed that the clupein molecule, which consists of arginin, serin, valin, prolin and alanin, is composed of a large complex of arginin groups with which smaller groups of amino-acids are associated in the proportion of 2:1. On heating clupein 80 minutes with sulphuric acid (4% by volume) to 160° the biuret reaction disappears. In the reaction liquid are found, besides free arginin and free monamino-acids, peptid-like substances containing at least two linked arginin molecules—probably arginin hydrid. According to this a diarginid group is to be assumed in the protamin molecule. By precipitation with phosphotungstic acid in alcoholic solution it is possible to separate the free arginin from the arginin peptids or from the diarginids and polyarginids. M. Nelson-Gerhardt's observation, which showed that the monamino-acids in clupein are also combined, is confirmed.

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**Digestion of Histon Sulphate with Peptohydrochloric Acid.**

*K. Felix, Ztschr. f. physiol. Chem., Berlin, 120:94, June 1, 1922.*

Recent investigation of protein seeks to resolve albuminous substances into individual considerable fragments in order to elucidate in this manner the arrangement of the individual amino-acids in the whole molecules. In this way there were isolated by hydrolysis from protamins substances whose relation to the protamins resembles that of peptones to albumin. It was of importance, therefore, to determine whether the nearest related substances to protamins, namely histons, behave similarly. Kossel isolated histopepton from the mixture of the digestive products of histons produced by pepsin by precipitation with sodium picrate in weak alkaline solution. But in addition to histopepton

another unknown substance is precipitated by sodium picrate which is removable by precipitation with silver and barium. The question arises as to what these bodies precipitated by silver and barium represent.

The analyses of the individual fractions show that histons are built upon quite a different principle from that for the protamins. In the former the whole molecule consists of different, in the latter of similar, large fragments. Accordingly, in this connection, histons stand between protamins and the more complicated albuminous substances. Obviously these fragments are preformed in the histon molecule and are liberated by pepsin digestion. How the assembling of these large fragments in the whole albumin molecule is to be conceived remains to be determined.

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**A Basic Peptone-Like Substance in the Thymus Gland.**

*K. Felix, Ztschr. f. physiol. Chem., Berlin, 120:91, June 1, 1922.*

Substances containing large amounts of peptone have been isolated from the intestinal mucosa, lymphatic glands and the thymus gland. In the preparation of histon from thymus gland, the preparation and analysis of such a substance was attempted. As it gave no diazo reaction histidin was absent, nor could lysin be detected with phosphotungstic acid. On the whole the substance was found to consist only of arginin and monamino-acids, thus resembling the protamins of the salmin group. Simple rough calculation showed 1 aldehyd. to be associated with 2 molecules of monamino-acids. This substance is therefore distinguished from the protons in that it contains 1 monamino-acids to 2 molecules arginin. Its composition is simpler than that of the substance obtained from lymphatic glands which contains lysin in addition. Whether it is related to Nelson's thymamin cannot be determined as the latter is not sufficiently characterized.

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**Urinary Proteinic Acids. I. Oxyproteinic Acid.**

*S. Edlbacher, Ztschr. f. physiol. Chem., Berlin, 120:71, June 1, 1922.*

According to the universally prevailing view the proteinic acids discovered by Bondzynski and Gottlieb are said to represent fragments of the large albumin molecules that have escaped the general decomposition in the organism, as was emphasized, for instance, by Fuerth. In addition to the oxyproteinic acid prepared by Bondzynski, antoxyproteinic acid and alloxypoteinic acid, as well as uroferrinic acid and Hary's acid belong to this group. The preparation of pure compounds is very difficult. The proteinic acids are probably related to the peptid-like substances isolated from urine by Abderhalden and Pregel, and possibly to the urinary coloring matter urochrome. The proteinic acids are of importance also because they are considerably increased in phosphorus poisoning and in carcinoma. The question of the neutral sulphur is likewise obviously related thereto.

The proteinic acids were isolated from the urine by acidifying the same, by precipitation of barium salts with alcohol and further precipi-

tation of the aqueous solution of the barium salts with aqueous lead acetate solution, whereby alloxypoteinic acid is precipitated as a lead salt. The filtrate is freed from lead with sodium carbonate and antoxypoteinic acid precipitated from the same with mercurous acetate in acetic solution. Oxypoteinic acid may be precipitated from the filtrate by mercurous acetate with a soda-alkaline reaction. The preparation of these fractions or precipitates showed barium oxypoteinate to possess all properties described by Bondzynski and Gottlieb. Free oxypoteinic acid was decomposed into several fractions which could be separated into urea and a carbohydrate which forms an osazone having the formula  $C_{16}H_{18}N_4O_2$  and melting point  $130^{\circ} C.$  and is presumably a tetrose. Treatment with alcohol and ether yields fractions whose properties coincide to a great extent with the substance designated urein by Mohr. Oxypoteinic acid certainly does not contain any hexone bases and at most traces of other amino-acids. Accordingly oxypoteinic acid probably contains urea as a structural unit. The prepared tetrose is the first naturally occurring tetrose to be demonstrated.

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#### Detection and Estimation of Monamino-Acids.

*R. Engeland, Ztschr. f. physiol. Chem., Berlin, 120:130, June 1, 1922.*

The detection and estimation of monamino-acids, whose investigation is rendered difficult by their easy solubility, was effected by converting them into betains, the reliability of the method being tested on glutin. For methylation dimethyl sulphate in methyl alcoholic solution, and for neutralizing the acid formed potassium hydroxid in 10% methyl alcoholic solution were employed. There followed acidification with hydrochloric acid, siphoning from the separated potassium and distilling off of the methyl alcohol. Finally the residue was concentrated to syrup consistency after repeated extraction with methyl alcohol and filtration, the residue taken up with a little water, strongly acidified with hydrochloric acid and mixed with saturated aqueous mercuric chlorid solution. The precipitate produced thereby contains the betain of the respective amino-acid. By introducing hydrogen sulphid into the dissolved mercurial betain compound, mercury was removed and filtered and the filtrate precipitated in 20% absolute alcoholic platinum chlorid solution. The platinum chlorid precipitate was dissolved in hot water, platinum removed with hydrogen sulphid, the filtrate of the platinum sulphid evaporated on the water bath, the residue precipitated in 30% aqueous solution of  $HAuCl_4$  and the gold chlorid salt employed for analysis. It is possible by this method to detect minute amounts of free amino-acids.

The detection of amino-acids in the blood was also attempted by this method. For this purpose the ascitic fluid was employed which, in cases of pure congestive ascites, free from pathologic elements, must contain all dialyzable constituents of the blood. The yield of betains was, however, very moderate. From 6.5 liters ascitic fluid there were obtained only 0.06 gm. betain of leucin, the betain of chloraurate, another betain, probably that of lysin (hexamethyllysin), and in addition

only a few milligrams tetramethylammoniumaurate, which probably originated from cleaved ammonia (perhaps from urea).

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**New Diamin Combinations.**

*Peter Bergell, Ztschr. f. physiol. Chem., Berlin, 120:220, June 24, 1922.*

Attempts were made to prepare combinations of amino-acids with aliphatic diamins, whose structure resembles that of polypeptids. It was attempted to obtain the preliminary stages of the simplest types of the desired combinations by the reaction of  $\alpha$ -halogenated fatty acid chlorids or bromids with those diamins. It was found possible to obtain  $\alpha$ -dibromopropionylpentamethylendiamin analytically pure in good crystals and of fair yield. Pentamethylendiamin hydrochlorate was dissolved in water, hydrochloric acid neutralized with KOH, and then normal potassium hydroxid solution and  $\alpha$ -propionylbromid were added in small portions with cooling and constant shaking. In a similar way  $\alpha$ -dibromisocapronylpentamethylendiamin is obtainable, possibly the preliminary stage of a dibenzylpentamethylendiamin. The  $\beta$ -naphthalinsulphochlorid method was employed by Emil Fischer for the preparation of fine crystalline derivatives of amino-acids. It has the advantage over the benzyl chlorid method that by the sulphur analysis or nitrogen analysis the attached aromatic rest is immediately differentiated from the parent body. There were prepared  $\beta$ -naphthalinsulphopiperidin, di- $\beta$ -naphthalinsulphopiperazin and di- $\beta$ -naphthalinsulphopentamethylenediamin. The preparation was carried out by dissolving the respective substance in water, pouring naphthalin sulphochlorid dissolved in ether over the same and adding 10% NaOH while shaking, whereupon the poorly soluble combination separated out.

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**The Capacity of Yeast to Split Acid Amids.**

*Walter Dieter, Ztschr. f. physiol. Chem., Berlin, 120:280, June 24, 1922.*

In fermentative albumin cleavage the occurrence of ammonia has been frequently observed. The source of the ammonia is found to be the  $\alpha$ -amino-groups of the amino-acids, on the one hand, and the amido-groups of the two acid amids, asparagin and glutamin, on the other. The latter may probably be regarded as structural components of albumin and not the amino-acids belonging to the same, which are the most easily isolated of the hydrolytic split products. The separation of the amino-group from the natural amino-acids takes place very readily in the organism. In the case of the acid amid group, ammonia is liberated by simple hydrolysis. Mold fungi and putrefactive bacteria split amids very easily. Macerated yeast juice was examined. Asparagin was selected as the split product. When the mixture remained sterile no ammonia cleavage occurred. Accordingly the experiments showed that top-fermenting pure culture yeast is unable to split off amido-nitrogen from asparagin and some other acid amids as long as

it ferments. In certain experiments cleavage occurred, which was probably brought about by infection with other microorganisms.

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**Yeast-Nucleic Acid, III.**

*H. Steudel and E. Peiser, Ztschr. f. physiol. Chem., Berlin, 120:292, June 24, 1922.*

In attempts to determine the composition of yeast-nucleic acid it was found that sodium guanylate could be obtained from pure sodium yeast-nucleate without further cleavage. Guanylic acid may then be obtained from sodium yeast-nucleate. The rest of the molecule of yeast-nucleic acid after guanylic acid has been separated cannot be identified precisely. Probably this rest consists of simple nucleic acid, but until that has been confirmed a constitutional formula for yeast-nucleic acid alone cannot be proposed. Thymus-nucleic acid has so far proved resistant to the action of alkalis. It must be assumed therefore that material differences exist between thymus-nucleic acid and yeast-nucleic acid, probably in the combining relations of the simple nucleic acids.

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**Observations on the Presence of the Antineuritic Substance, Water-Soluble B, in Chlorophyll-Free Plants.**

*C. R. Orton, E. V. McCollum and Nina Simmonds, J. Biol. Chem., 53:1, July, 1922.*

Wishing to determine whether in plant tissues the vitamin, water-soluble B, is associated directly with the chloroplasts, authors fed young rats a diet known to be deficient in water-soluble B vitamin, and when they developed characteristic symptoms the diet was modified by replacing one of its elements with the food substance to be studied. In this manner they tested for water-soluble B onion root, mushroom (*Agaricus campestris*), Indian-pipe (*Monotropa uniflora*) and a non-chlorophyll-producing parasitic plant (*Cuscuta gronovii*). They found onion root, a structure which contains no chloroplasts, to contain a certain amount of water-soluble B, and this, they believe, warrants the conclusion that water-soluble B is not concerned with the structure of the chloroplast. The mushroom proved to be a good source of water-soluble B. Indian-pipe, *Monotropa uniflora*, a nonchlorophyll-bearing plant, gave inconclusive results, as did dodder (*Cuscuta gronovii*); the death of experimental animals.

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**etic Acid as a Solvent for the Antineuritic Sub-Soluble B.**

*evine, E. V. McCollum and Nina Simmonds, J. Biol. ily, 1922.*

experiments rats were fed a diet which was complete bsence of water-soluble B. After decline had set in,

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the material which remained in solution when a filtered acetic acid extract of raw navy beans was poured into 5 times its volume of ether, was given to the rats. The amount administered was equivalent to 50% of beans in the diet. The animals responded in the same manner as if a liberal amount of a natural food containing water-soluble B had been made to replace half of their experimental diet. The authors conclude that glacial acetic acid is the best organic solvent which they have as yet found for the extraction of water-soluble B from plant materials. The active glacial acetic acid extract can be further concentrated by the removal by precipitation with ether of a large quantity of inactive material.

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**Acidity Conditions and Sensitiveness to Temperature of Invertin.**

*Hans v. Euler and Karl Myrbäck, Ztschr. f. physiol. Chem., Berlin, 120:61, June 1, 1922.*

The occurrence of an acidity maximum of enzyme activity may be deduced from the electrolytic character of invertin or of the combination invertin-cane-sugar. In this case invertin functions as an acid, cane-sugar as a base, or perhaps inversely, so that the molecule compounded of invertin-cane-sugar may be regarded as an amphoteric electrolyte. As regards cane-sugar, its properties are predominately acid; its dissociation constant, according to Michaelis, is  $2.4 \times 10^{-13}$ . A smaller dissociation constant certainly corresponds to the basic properties of cane-sugar. It is to be assumed that cane-sugar also reacts in enzymatic cleavage, not as an acid but as a base, or as a neutral molecule. Regarding invertin Michaelis founded his assumption that it functions as an acid on the fact that this enzyme is adsorbed by basic but not by acid adsorbents. The experiments were therefore directed toward ascertaining whether the experimentally determined curve, i.e. the one with a maximum at  $\text{pH} = 4-5$ , is due to invertin itself, or whether this acidity optimum changes greatly with an increasing degree of enzymic purity. It was found that the much more highly purified enzyme yielded the same acidity maximum and the same acidity curve as the enzyme previously investigated, which certainly contains large amounts of yeast gum and probably of other substances. The same enzyme solutions with which the last mentioned acidity curve was investigated were employed also to measure the invertin's sensitiveness to temperature with optimum acidity ( $\text{pH} = 4-5$ ), in order to determine whether the invertin stability had diminished considerably after a substantial part of the impurities previously associated with it had been removed. It was shown that the stability of the purest preparation was strikingly high. Accordingly a substance which impairs stability has apparently been removed by purification.

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**Blood Invertin and Antigenic Properties of Yeast Invertin.**

*E. Knaffl-Lenz, Ztschr. f. physiol. Chem., Berlin, 120:110, June 1, 1922.*

As shown by Weinland the blood of very young animals gains the ability, upon cane-sugar injections, to invert cane sugar. The occur-

rence of an inverting ferment in the blood following injections of cane sugar is of theoretic interest as far as concerns the question as to whether a new foreign ferment is formed as a result of sugar injection, or whether this ferment is identical with intestinal invertin, which enters the blood owing to the injection. It was decided to compare the physical and chemical properties of blood invertin and of intestinal and yeast invertins to demonstrate the identity or relation of these ferments with the aid of serologic methods.

Schütze and Bergell were able to obtain a serum by invertin injection which diminished the effect of invertin. With the aid of such antiferments it should be possible to test ferments regarding their identity, not only by experiments in vitro, but also by determining whether a rabbit immunized with yeast invertin is still able to furnish an active serum after cane-sugar injections. The present researches failed to answer this question satisfactorily, as on the one hand the rabbits did not yield an inverting serum following cane-sugar injection, while on the other immunization with highly active and highly purified yeast invertin preparations yielded only a serum that diminished the invertin effect inconsiderably. The chief causes of the slight success of immunization with ferments are discerned in their easy destructibility, their slight resorptive capacity and their fixation by circulating albuminous substances and carbohydrates before they can react with the cells. The experiments showed that the arresting action of the serum of previously treated rabbits does not differ materially from that of the normal serum. It is highly probable, therefore, that invertin does not act as an antigen and that previous treatment merely renders active those substances that are contained normally in varying amount in the serum. A series of observations has shown that the injection of any colloidal substances alters the serum's reacting capacity, by which specific antibody effects may be simulated.

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**Regeneration of Diastase and Its Dependence on Oxygen.**

*W. Biedermann, Biochem. Ztschr., Berlin, 129:582, May 23, 1922.*

As the only organic substances, besides traces of albumin, contained in human parotid saliva are amylose, maltase, and peroxidase, it was assumed that pure diastase could be prepared most easily from this form of saliva. But mixed human mouth saliva contains only mucin in addition. The mucin is separated with alcohol, and a water-soluble substance remains behind in the solution which is demonstrably the seat of the fermentative action. This substance yields all albumin reactions but shows at the same time the characteristic behavior of an albumose and is also precipitated by strong HCl; the clouding that forms disappears on heating and reappears on subsequent cooling. A specific albuminous substance is therefore involved whose aqueous solution possesses extremely strong diastatic action and shows very characteristic behavior on being heated gradually, in that it clouds between 70-80° C. from the separation of coagulated albumin. However, an albumose-like residue remains in solution whose presence in the filtrate is always easily detectable.

Investigations show the diastatic ferments to possess an extraordinary  
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narly complex character, the organic fundamental substance being entirely inactive in itself and requiring, unconditionally, certain salts for its activation with which it manifestly enters into characteristic complex combinations. But, in the activation of diastase, the H-ion concentration, the temperature and also the amount of ferment and the acid-combining capacity of the ferment's organic basis play an essential part. Oxygen likewise is important in the diastatic action. Unboiled amylose solution agitated with air yielded the achromatic point at 45° after only about 15 minutes, while the otherwise precisely similar but oxygen-free sample reacted pure blue on addition of iodine, even after several hours. The deeply depressed diastatic power of saliva heated to the boiling point is regenerated to a high degree simply by the addition of oxygen. Therein, however, the finely divided coagulated albumin obviously plays an essential part. Salivary diastase is not destroyed entirely under brief action of the boiling temperature. A residue remains which is able to exercise very powerful diastatic action in combination with oxygen, without which, however, it exhibits merely traces of enzymotic power even under the most favorable conditions. Warming the ferment solution to 70° or 80° results in a very considerable and permanent diminution of diastatic power. With a further rise in temperature this power remains fairly constant until, finally, it again becomes strikingly diminished at about 95°. This, unlike the first loss of strength, is not related to an actual injury, i.e. to substantial alteration of the organic basis, but is merely due to oxygen deficiency. The researches show that the physically absorbed oxygen does not govern the activation of the albumose-like ferment residue, but that oxygen is bound to the ferment in some way and that this bond is severed only at a temperature close to the boiling point.

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**A Study of the Acetone and Butyl Alcohol Fermentation of Various Carbohydrates.**

*Guy C. Robinson, J. Biol. Chem., 53:125, July, 1922.*

In the author's work these carbohydrates were studied: (1) Monosaccharids—xylose, arabinose, glucose, fructose, mannose and galactose. (2) Disaccharids—sucrose, maltose, lactose, melibiose and trehalose. (3) Trisaccharids—raffinose and melezitose. (4) Polysaccharids—starch, dextrin and inulin. In addition the 2 alcohols, glycerol and mannitol, were investigated. A number of sugar mixtures were also submitted to fermentation in order to study the behavior of the organism with respect to sugar preference, if any existed, when both monosaccharids and disaccharids were offered. In these experiments the course of the fermentation was followed by determinations of the titratable acidity at periodic intervals. Sugar determinations were likewise made throughout the fermentation period in order to observe the progress of carbohydrate consumption and to ascertain, if possible, the exact method by which each compound was utilized by the organism. The specific organism employed in the fermentations was a pure culture of a granulobacter type of organism.

The tabulated results show that the fermentations obtained with the various carbohydrates used in this investigation are of 2 types. The

first type, to be regarded as the normal, is characterized by a decided fall in the acidity after the maximum is reached, and also by the complete consumption of the carbohydrate. The group of abnormal fermentations is characterized by the persistence of a high acidity and also by the incomplete destruction of the carbohydrate. Glucose, fructose, mannose, sucrose, lactose, and starch belong to Group 1, while galactose, xylose, arabinose, raffinose, melezitose, inulin, and mannitol constitute Group 2. Dextrin belongs to either group depending upon the method used in the preparation of the sample fermented. Trehalose, rhamnose, melibiose, and glycerol are not fermented. The butyl organism secretes the enzymes amylase, inulinase, and maltase; but it does not secrete sucrase, lactase, or raffinose. Raffinose is hydrolyzed within the cell by means of sucrase into melibiose and fructose. The organism first completely removes the hexoses, with the exception of galactose, from mixtures also containing sucrose and lactose. Maltose on the other hand is fermented concurrently with glucose, fructose, or mannose.

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**The Fermentation of Hexoses and Related Compounds by Certain Pentose-Fermenting Bacteria.**

*W. H. Peterson, E. B. Fred and J. A. Anderson, J. Biol. Chem., 53:111, July, 1922.*

In the authors' experiments the kind of culture medium, the type of fermentation flask, and the methods of analysis for the different fermentation products were those described in previous papers. In most of the fermentations the acids formed were neutralized by the addition of sterilized 1.0 n. sodium hydroxid. Four cultures of pentose-fermenting bacteria and a strain of *Streptococcus lactis* were used in this work. The fermentation products formed by this group of pentose-fermenters from glucose, fructose, lactose, raffinose and melezitose were determined. All of these compounds were converted almost quantitatively into lactic acid, which latter represents 90% or more of the sugar fermented. The fermentation products of *S. lactis* like those of the pentose-fermenters were modified by the structural configuration of the fermented compound. The pentose-fermenters produced only the inactive form of lactic acid while the active isomer was the form produced by the strain of *S. lactis*. Fractional crystallization failed to show any mixture of the 2 forms in any case.

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**The Heat of Combustion of Lactic Acid.**

*Otto Meyerhof, Biochem. Ztschr., Berlin, 120:594, May 23, 1922.*

The heat of combustion of lactic acid was determined according to Longuinine's formula: heat of combustion of the ester — heat of combustion of alcohol — 2000 cal. = heat of combustion of the acid. Per mol 329,509, and per gm. 3661 cal. were obtained. The determination was carried out with Berthelot's bomb whose gage value was first ascertained by combustion of benzoic acid and cane sugar. For 1 gm. cane sugar 3952 cal., for benzoic acid 6325 cal. and for anhydrous zinc lactate 2597 cal. were obtained. For the control the heat of dilu-

tion of lactic acid was also determined. The total heat of dilution of the 9% acid (n.) was 4.1 cal. per gram. Solution of 0.265 gm. zinc oxid in 100 c.c. 0.1 n. HCl yielded 73.0 cal.; per gram 276 cal, and per mol 22,400 cal. With anhydrous zinc lactate in water or HCl, 27.8 cal. per gram zinc lactate and 6800 cal. per 1 mol were found. From glycogen preformed in the muscle as well as from added glycogen lactic acid is formed which passes into the sodium phosphate solution serving as the suspension fluid, with which it is converted according to the equation:  $\text{Na}_2\text{HPO}_4 + \text{HL} = \text{NaL} + \text{Na}_2\text{PO}_4$  (L = lactic acid anion). Here, on the average, 201 cal. per gram lactic acid appear (6 experiments gave between 180 and 219 cal.).

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### **Enzymatic Fat Synthesis.**

*L. Spiegel, Ztschr. f. physiol. Chem., Berlin, 120:103, June 1, 1922.*

Enzymatically influenced processes belong to the reversible ones in conformity with the experiences of pure chemistry, as appears already from Bourquelot's glucosid syntheses. The formation of fats in the plant is also manifestly attributable to enzymatic processes and for a part of it, namely, the combination of glycerin and fatty acids, that has already been demonstrated. After the occurrence of fat-splitting enzymes (lipases) in the oil-bearing seeds, especially in castor-oil seeds, had been proved, attempts were made to realize the reversal of the process.

The system's freedom from water is generally considered a condition for fat synthesis. If water be added to the fat mixture fat cleavage sets in promptly, which may, as is known, proceed to such an extent as to render possible the technical winning of glycerin from fats. In seeds, however, not only the combination of glycerin and fatty acids takes place, but also the formation of these components. It was sought to ascertain whether these processes can take place apart from the vital function. The experiments were commenced with cellulose as raw material. The seeds of white mustard were employed as the ferment source. These experiments unquestionably showed the formation of fatlike substances as was proved by extraction with ether. Oxygen was not concerned therein; when the liquid was in contact with air or a hydrogen atmosphere the yield was not affected, while a carbon dioxid atmosphere reduced it. The same experiments were conducted with seeds of the sunflower, cabbage and white poppy. For the remaining experiments starch and glucose were employed. Acidulating with acetic acid favored the process. The capacity for forming fat seems to increase with increasing maturity and to disappear at full maturity. The observed experimental procedure is, however, unsuitable for the production of considerable amounts of fat, as the end-link of the synthesis, esterification, requires water-poor mediums.

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### **Researches on Bile Acids. XII. Ciloidanic Acid.**

*Heinrich Wieland and Otto Schlichtung, Ztschr. f. physiol. Chem., Berlin, 120:227, June 24, 1922.*

Progressive oxidation of bilianic acid yielded biloidanic acid, cilianic acid and ciloidanic acid. Ciloidanic acid was prepared by pour-



ing nitric acid over cilianic acid, the latter dissolving in the cold. The mixture was warmed 10 hours and on standing the crystalline mass separated. Ciloidanic acid is readily soluble only in water.

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**Researches on Bile Acids. XIII. Decomposition of Iso-desoxybilianic Acid. A Contribution to Determination of Position.**

*H. Wieland and F. Adickes, Ztschr. f. physiol. Chem., Berlin, 120:232, June 24, 1922.*

Isodesoxybilianic acid is formed in addition to desoxybilianic acid in moderate oxidation of desoxycholic acid either by permanganate or nitric acid. In distillation in high vacuum two different finely crystallized pyro-acids are obtained by a smooth reaction from the two acids, which are isomeric diketocarbonic acids,  $C_{23}H_{34}O_4$ . Pyro-isodesoxybilianic acid,  $C_{23}H_{34}O_4$ , is easily converted by permanganate into a ketotricarbonic acid,  $C_{23}H_{34}O_7$ , which is isomeric with the open pyrocholoidanic acid, without the simultaneous formation of carbon dioxide. As with the formation of choloidanic acid from desoxybilianic acid, so norcholoidanic acid is obtained from ketotricarbonic acid. While choloidanic acid could be converted quite smoothly under thermal decomposition with attachment of  $CO_2$  and  $2 H_2O$  into pyrocholoidanic acid, norcholoidanic acid was found to be refractory to this reaction, although it loses fairly accurately one molecule  $CO_2$  and one molecule  $H_2O$  at  $280-290^\circ$ . The dimethyl ester of the acid which was introduced into the pyro-reaction could be distilled for the most part undecomposed, being simply transposed into an isomerid of different configuration.

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**The Calibration of the Osterhout Respiratory Apparatus for Absolute Quantities of Carbon Dioxid.**

*G. H. Parker, J. Gen. Physiol., 4:689, July 20, 1922.*

The Osterhout apparatus consists of a closed system in which the air is made to circulate by means of a pump. The air passes from a chamber in which the organism is confined and in which consequently the carbon dioxide is produced, either directly to a glass tube containing an indicator in solution or indirectly to this tube through a U-tube filled with fragments of sodium hydroxide. In taking readings with this apparatus the time in seconds required for the indicator to change from one tint to another as compared with standard solutions of known pH value is recorded and the rate of this change is assumed to be identical with that of the excretion of carbon dioxide by the organism.

After various attempts, Parker finally adopted as a method of calibration that of making mixtures of carbon dioxide and atmospheric air and of introducing them at a known rate into the apparatus in place of the organism. Thus a constant and measurable supply of carbon dioxide was substituted for that produced by the organism. In this

form of procedure the rate of change in the indicator corresponded very closely to the rate of introduction of carbon dioxide. The indicator used was an aqueous solution of phenolsulphonephthalein, and the times in seconds necessary to change its tint from that characteristic for pH 7.78-7.36 at the 4 concentrations of carbon dioxide used, are tabulated. The steps necessary to determine the amount of pure carbon dioxide in ten-thousandths of a milligram delivered per second to the apparatus are also shown. A table gives the percentage concentration of the carbon dioxide mixture, followed by the time required to deliver 10 c.c. of this mixture to the apparatus. By dividing 10 c.c. by the number of seconds needed to deliver that amount of gas to the apparatus, the volume of gas delivered per second was found. By multiplying this volume by the appropriate percentage of the impure carbon dioxide contained in the given mixture, the several volumes of impure carbon dioxide delivered were determined. By absorbing with sodium hydroxide in a graduated tube a sample of the carbon dioxide used, it was found that this gas was pure to the extent of 97.2%, and on introducing this correction into the calculation, the volume of pure carbon dioxide delivered per second in each of the 4 tests was calculated. To change the quantitative determinations of carbon dioxide from volumes to weights, the volumes of this gas in cubic centimeters were multiplied by 1.75984, the weight in milligrams of 1 c.c. of carbon dioxide at 24° C. and 762 mm. of barometric pressure, the conditions of the test. The result of this operation was then multiplied by 100,000 to permit the final number to be expressed in hundred-thousandths of a milligram. In this way the weight of carbon dioxide delivered per second and expressed in hundred-thousandths of a milligram was arrived at.

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#### Chlorin Estimation in Organic Material.

*Stefan Bogdándy, Ztschr. f. physiol. Chem., Berlin, 120:30, June 1, 1922.*

A method of chlorin estimation in organic material was proposed which yields correct values and possesses the additional advantage that it enables nitrogen and another ash constituent to be estimated in the residue. It consists essentially in wet incineration of organic matter and the driving of the liberated hydrochloric acid into a silver nitrate solution, similarly to Kjeldahl's method. Incineration by sulphuric acid containing potassium sulphate and cupric sulphate occupied about 1½ hours with air suction. In general the methods making use of destruction of the organic matter deserve preference over those in which albuminous substances are precipitated as described by Larsson, McLean, Van Slyke and Rogée. Incomplete wet incineration of organic matter is practiced in those methods which consist in the solution of organic matter by heating with nitric acid. Such a one, described by Koranyi, yields correct values for plasma and serum but is not generally applicable. As regards wet incineration the method, made known by Emde, with sulphuric acid and chromic acid is mentioned specially. Of dry incinerations a method recommended by Cameron and Hollenberg is capable of yielding good results if it is controlled by means of comparison with

a standard method or by addition of known amounts of sodium chlorid to the experimental substance.

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**A Modification of the Bell-Doisy Phosphate Method.**

*A. P. Briggs, J. Biol. Chem., 53:13, July, 1922.*

An objection to the colorimetric phosphate method of Bell and Doisy is that the alkaline blue color which is used for comparison in the colorimeter fades rather rapidly, so it is not advisable to read more than about two determinations against the same standard. Briggs observed recently that when a little sodium sulphite is added to an acid solution containing phosphate and molybdate the subsequent addition of hydroquinon caused the formation, not of a green, but of a blue color of an intensity considerably greater than the green. This color does not depend upon reduction of the molybdic acid by  $\text{SO}_2$ , since sodium sulphite, hydroquinon, and acid molybdate solutions when mixed give no color. The use of these modifications gives a clear blue, nonfading color for comparison, the proportionality of which is exact over a wide range. The intensity of the color allows the determination of phosphates in 1 c.c. of plasma. The following technic is that used for blood or plasma: A measured volume of plasma is transferred to a small Erlenmeyer flask, diluted with 3 volumes of water and 1 volume of 20% trichloroacetic acid. The flask is stoppered with the thumb, shaken vigorously for a few seconds, and after standing about 10 minutes, the contents are transferred to a dry ashless filter. The filter funnels rest in long pyrex test-tubes and are covered by watch glasses to prevent loss by evaporation. For the standard, transfer 2 c.c. of the diluted phosphate solution to a similar flask or tube; then to each add 2 c.c. of the molybdate solution, 1 c.c. of the sodium sulphite solution, and 1 c.c. of the hydroquinon solution, and dilute with water to the mark. Allow the tubes to stand about 30 minutes for color production and compare in the colorimeter.

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**Detection of Vernin.**

*H. Steudel and R. Freise, Ztschr. f. physiol. Chem., Berlin, 120:126, June 1, 1922.*

Vernin is detected with difficulty in extracts of vegetable and animal organs or in decomposition fluids obtained from physiologic substances, as it first separates in a gelatinous form and does not crystallize easily. A silver and a picric acid compound of crystallizing vernin have hitherto been described. The attempt was therefore made to prepare a product, not readily soluble, by acylation, similar to Haiser and Wenzel's preparation of inosite. To do this, 2 gm. vernin, melting point  $240^\circ \text{C}$ ., were mixed with acetic anhydrid and granular sodium acetate, by which everything is dissolved. Excess acetic anhydrid was distilled off in vacuo and the residue dissolved in chloroform. The substance so obtained forms fine crystals, has three acetyl groups, is optically active and melts at exactly  $226^\circ \text{C}$ .

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**On Iron Salts of Dipyrrolylphenylmethane Dyes and on Triphenylpyrrolylmethane. II. Diphenylpyrrolylcarbinol and its Conversion Products.**

*Hans Fischer and Maria Kaan, Ztschr. f. physiol. Chem., Berlin, 120:267, June 24, 1922.*

Statements hitherto made regarding dipyrrolylphenylmethane dyes have shown many analogies with triphenylmethane dyes with one essential difference. It has not been possible so far to obtain carbinols that are converted into dyes upon treatment with acids. This has now been accomplished in the diphenylpyrrolylmethane series. With the aid of Grignard's reaction the finely crystallized carbinol 1 was synthesized in the cold from dimethyldicarbethoxypyrrol and phenylmagnesium bromid. This is characterized by a finely crystallizing picrate. Further, there were prepared: p-bis(2.4 dimethyl-3-carbethoxypyrrolyl)-methyl anisol, with a melting point of 170°, and p-bis(2.5 dimethyl-3-carbethoxypyrrolyl)-methyl benzaldehyd having a melting point of 270°.

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**An Apparatus for Macroscopic Cataphoresis Experiments.**

*John H. Northrop and Glenn E. Cullen, J. Gen. Physiol., 4:635, July 20, 1922.*

The authors illustrate and describe a form of apparatus which they found to be very convenient for the determination of the migration of fine suspensions in the electric field. It differs essentially from the usual cataphoresis apparatus in that the whole is inverted so that the central portion, which contains the suspension to be studied, is above the heavier electrode solutions and may be left open. This increases both the convenience and accuracy of method since (1) a greater latitude in concentration of solution is allowed, (2) the boundaries may be adjusted more exactly, and (3) the solution may be renewed without disturbing the electrode solution. The zinc electrodes are put in place with rubber stoppers, the tube is clamped in a vertical position, and the apparatus is filled with saturated zinc sulphate. The three-way stop-cocks are then closed and the zinc sulphate in the upper part of the cell is washed out through the "tail holes." The tubes above the stop-cocks are now filled with 0.1 m. sucrose solution containing the same concentration of electrolyte or other substance as is to be used with the suspension. The sugar solution is then allowed to run out until the level reaches the small tube connecting the funnel and the U-tube. The suspension is then added and the level adjusted carefully by means of the stop-cocks so that the line of demarcation is opposite one of the graduations on the side arms. The upper stop-cock is then closed and the lower ones are opened so as to connect the zinc sulphate with the sugar solutions. The current is applied and the distance traversed by the boundary determined after a convenient interval. Since the cell is of uniform diameter the drop in potential is determined simply by dividing the total voltage by the distance between the three-way stop-cocks. Concerning the influence of the voltage the authors found

that the rate of migration was directly proportional to the voltage between the limits of 1-4 volts per centimeter, provided the experiment was not allowed to run too long. At low voltages, the rate of migration remained constant until the boundary approached the zinc sulphate, but if the potential drop was increased beyond 2 volts per centimeter, it was found that the boundary moved at the proper rate for the first 4-5 mm., but then became much too slow on one or both sides. The presence of sugar greatly facilitated the adjustment and maintenance of a sharp boundary line. No effect on the velocity of migration could be observed up to 0.5 m. Higher concentrations than this decreased the velocity presumably on account of the viscosity.

### 1c. PHARMACOLOGY AND TOXICOLOGY.

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#### Problems of General Pharmacology.

*Heubner, Klin. Wchnschr., Berlin, 1:1289, 1349, June 24, July 1, 1922.*

We now know that many vital processes are essentially of a colloido-chemic nature, as for example the contraction of muscle, which is a swelling process; the excitation of a cell complex is differentiated from a condition of rest by the loosening of the cell colloids. A colloido-chemic condition is characterized by the degree of division, that is the number of molecules in a particle of the colloid system, by the power with which these particles act upon one another and upon the water lying between them; if these particles do not interfere with one another in their motility, the system has the character of a fluid—a sol, but if they interfere with one another to a certain extent, so that the system still possesses elasticity but has form, it has the character of a solid substance—a gel; both conditions may show transitions into each other. The protoplasmic current shows the sol condition of the protoplasm and can sometimes be made to stand still reversibly. As a result of the gathering of several colloid particles there can also result a limitation of the motility, which is seen in sols as well as in gels as a cloudiness. The attraction powers of the colloid for water depend upon the chemical nature of the synthetic substances and upon the presence of a third substance, namely the ions of electrolytes, which are held fast by the colloid particles by absorption, and transmit the electric charge to them. This absorptive power of the colloids is also extended to food substances and drugs, and the extent of such absorptive combinations depends upon the capillary activity of the substances entering them.

The relations between colloid particles and soluble substances control the synergism of form and chemistry in a reciprocal manner. The colloidal structure acts upon the chemical transposition by retardation of the diffusion, and by absorption it leads to the concentration of certain substances to a narrow realm. The effect of the colloids upon the diffusion controls the permeability. The diffusion in pure sol, and even more in pure gel, is considerably retarded in contrast to diffusion in a crystalloid solution, and to this should be added the absorption in



the colloid particles, which holds the diffusing molecules fast. Variations of permeability are produced by changes of the colloidochemic condition; in swelling the permeability is greater than in gelatinization. The rapidity of diffusion represents a measure of the biochemic transpositions in the body. These transpositions, of their own accord, lead to effects on colloidochemic processes by an increase of H-ions, as in muscular contraction. The reciprocal relations between true chemical reactions and colloidochemic processes explain the relation between function and change of form. As the 2 extreme poles of pharmacologic effects, such effects should be mentioned as rest upon a true chemical reaction, as for example, the caustic and disinfecting action of the halogens and of the oxidizing remedies, oxalate poisoning, the effect of many blood poisons (carbon monoxid, nitrobenzol) and those in which there is only a coarse mechanic expression of power, namely an absorption at the bordering surface of a phase. The latter should be attributed to the catalyzators, which by their mere presence accelerate or retard the course of a reaction—positive or negative catalyzators—without being changed themselves by the reaction.

The rapidity and strength of a reaction depend upon the concentration in the free solution or on the surface, for which reason many substances act catalytically only in the finest division, therefore with a large surface, as charcoal. An increased temperature and radiation accelerate the course of the reaction by acceleration of the molecular motion. The internal friction of the medium also has an effect upon molecular motion; substances in solution may act as negative catalyzators by their presence. Many substances found in solution have a varying tendency to become absorbed and different absorbents have different powers to bind substances, which is caused by chemical elective relationships. Aside from the true chemical affinity of the atoms, there is also a residual affinity of the molecules, as in oxyhemoglobin. The decision whether it is a matter of absorption or chemical binding is not always easy and the attraction power between hydrophil colloids and water falls into this border region. There must also be added the electric attraction power not only for the chemical transpositions of the electrolytes, but also for the organic reactions, and finally, absorptive and true chemical combinations may be bound up with simple conditions of solution, which is the case in most of the pharmacologic effects. The balance between the colloid molecules among themselves and their power of attracting water are disturbed by colloidochemic changes. In this group belong the effects of the salt ions, of calcium, magnesium, bromid, etc., of the alkalies and, to a less extent, of acids. The astringents act through gelatinization of the cell content and the action of phenol is through the coagulation of albumin. The indifferent narcotics and terpin derivatives cause primary colloidochemic changes.

The colloidochemic theory, according to which the normal nerve excitability is inhibited by a solution of the narcotically acting substances in the heterogeneous lipid phases, is in complete consonance with the physiologic observations, which make a loosening of the biocolloids during the excitation likely. Colloids weaken the action of many poisons. The saponins, digitalis glucosids and many alkaloids also seem capable of colloidochemic actions. The diuretic effect of purin derivatives is explained by the diminution of the swelling tension.

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**Chemical and Pharmacologic Synergy.**

*Fühner, Münch. med. Wchnschr.*, 69:915, June 23, 1922.

Considering the synergy of 2 drugs or toxins as referring to their reciprocal increased activity, only a synergy at the identical site of the result can be called true synergy, and this is best sought in isolated organs. No general rules can be made for the occurrence of synergy; the effect is always specific, varying with different substances. One can only speak of a synergy of 2 remedies in the animal body when both substances enter into a firm chemical combination with each other, the combination being more effective than its components acting separately.

Not only complicated organic combinations like adrenalin come up for consideration as synergists of drugs which are introduced into the body, but also inorganic salts. In this way calcium has a significant action in the therapeutic effect of digitalis. Other synergists found in the body are cholesterin and lecithin. Of the latter we know that some substances act hemolytically only in its presence, and of the former, that it enhances the action of pilocarpin on the intestine. The products of the internal secretions of the body also come up for consideration as synergists of the organism. Especially significant is the synergism of morphin and the antagonism of acetonitril toward the iodine-containing combinations of the thyroid gland. These represent albuminous commercial products in the form of iodothyron and thyraden, which recently have been derived in a chemically pure form as crystalline thyroxin. The thyroid gland preparations are characterized by their well-known action of increasing the destruction of fat and albumin in the body and, on the other hand, of inhibiting the splitting of other substances, like carbohydrates. On feeding thyroid gland, the destruction of morphin and acetonitril is inhibited. This produces an increased toxicity of morphin, but a diminution in the action of the acetonitril, which otherwise is expressed in the splitting off of free hydrocyanic acid. Great significance should be attached to the decomposition products of the cell constituents. The synergistic effects with drugs of substances of intermediary metabolism like histamin, tyramin, guanidin and other proteogenic amines, are partly known; the same applies to cholin and its esters.

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**The Rôle of Protective Colloids in Colloidal Metal Solutions. Study of the Pathology of the Capillary System and of the Iron Reaction.**

*Rudolf Nissen, Ztschr. f. d. ges. exper. Med.*, Berlin, 28:193, June 7, 1922.

Rabbits received intravenous injections of various colloidal metal solutions, namely, electrocollargol (Heyden), electroferrol (Heyden), iron arsenite (Heyden) and lithiocarmin simultaneously; protective colloid (catalytic agent, Heyden); and protective colloid (Heyden) made of vegetable gum. In every instance but one, the injections produced an initial leukopenia followed by leukocytosis; in the exceptional case—injection of the protective colloid, catalytic agent, Heyden—there was moderate leukocytosis without a preceding leuko-

penia. The injections of mixtures of colloidal solutions and pigments were followed by clearly discernible evidences of capillary block. The avidity of the various tissue cells and systems was different within the same system; such avidity depending on: (1) the chemical composition of the material introduced by injection (acidity or alkalinity), which is stored in the plasma cells and at times even in the granules of the latter; (2) the degree of diffusibility of the colloidal solution injected; and (3) the conditions of blood stasis in the various organs.

Attempts were made to confirm these assumptions through deposition experiments: (1) of electrocollargol (in most minute particles); (2) of collargol (Heyden) in larger particles; and (3) of India ink. Substances of very high diffusibility, like lithiocarmin, are stored in the spleen, bone-marrow and lymph nodes; substances more difficult of diffusion resort to migration (a sort of pseudodeposition) to distant organs and deposition therein; this occurs mainly in the lungs, to a lesser extent in the liver, but never in the lymph nodes.

In some of the animals who had received iron there was obtained the Prussian blue reaction from the tissues. It also became evident that the difference in diffusibility of the colloidal iron in solution affects the onset and extent of ionization, hence also the onset of a positive iron reaction. The colloidal metal solutions introduced into the body must first undergo a certain modification within the tissues before they are able to give a positive iron reaction. Colloidal solutions not containing protective colloids (e. g., saccharated ferric oxid) yield a positive reaction immediately.

Concerning the staining properties of the blood pigment, it appears probable that certain changes, dependent upon and caused by changes in the colloidal structure of the pigment itself, determine positive or negative iron reactions in the iron deposits.

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**On the Influence of Colloids on the Action of the Non-colloidal Drugs. V. A Further Analysis of the Augmentor Effect of Lecithin on the Action of Pilocarpin.**

*W. Storm Van Leeuwen and A. V. Szent Györgyi, J. Pharmacol. & Exper. Ther., 20: 1, Aug., 1922.*

The action of pilocarpin could nearly always be augmented by the addition of small amounts of kephalin or of an ultrafiltrate of kephalin emulsions, doses of 0.1 c.c. of a 0.25% solution being usually sufficient to produce the desired effect. Sometimes larger doses—0.5 c.c. of the same emulsion—were necessary. The amount of active substances present in the ultrafiltrates could only have been very small. Pure lecithin had no influence on pilocarpin action. In 1 case there was a decided influence. The lecithin emulsion used in that particular experiment had been kept in a glass flask in the laboratory for 3 days, and may have deteriorated. The next day, however, the same emulsion was without any effect on pilocarpin action. Histamin action was mostly augmented by the addition of pure lecithin. This augmentor effect was distinctly present in 5 cases and absent in 1. However, it was never so marked as the kephalin augmentor action on pilocarpin. The influence of kephalin on histamin action was tested only twice, and was

positive in both cases. The most important point is that the ultrafiltrate of kephalin, which was nearly always active on pilocarpin, was negative on histamin. In 1 case it seemed to exert a slight augmentor action. Cholin action was not augmented by lecithin, but sometimes by kephalin and by ultrafiltrate of kephalin. The authors conclude that kephalin emulsions contain at least 1 substance which augments the pilocarpin and cholin action on smooth musculature, and 1 substance which stimulates the gut. Preliminary experiments have made it probable these substances are not identical.

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**Action of Atropin on Pulse and Blood Pressure.**

*O. Platz, Ztschr. f. d. ges. exper. Med., Berlin, 28:81, June 7, 1922.*

In the course of experimental observations on vagotonia and sympatheticotonia in the sense of Eppinger and Hess, as well as on the effects of atropin on electrocardiograms, the author noted that frequently following injections of atropin there was a slowing of the pulse, instead of the expected acceleration. He naturally assumed that this variation in effect was due to the different dosage and varying method of administration of atropin. With a view to confirming this assumption he undertook systematic experimental study of the phenomena, following great variations in dosage and indiscriminate subcutaneous, intramuscular and intravenous administration. In the subcutaneous and intravenous injection cases the author directed his observations mainly to the pulse reactions. By whatever method of administration, the dose given varied from 0.05 to 1 mg. In 24 of the cases, immediately following subcutaneous administration of atropin, there was slowing of the pulse, continuing throughout the experiment in all cases where the dose of the drug was not higher than 0.5 mg.; with doses higher than 0.5 mg. there ensued undoubted tachycardia.

Intravenous injections of atropin in doses up to 0.4 mg. resulted in similar effects; with higher dosage there was acceleration of the pulse without previous slowing. This slowing of the pulse following administration of atropin is attributable to a stimulation of the vagus; depression and paralysis of the latter follow only the intake of larger amounts of the drug or very rapid absorption. A fall in blood pressure followed for the most part only intravenous injections.

The question as to the proper dosage of atropin is not only of theoretic import, but entails also considerable practical significance, since it is evident that only very small doses of the drug are to be administered whenever we desire to effect a synergistic reinforcement of the diastolic action of small doses of digitalis. Strict watchfulness is enjoined in the dosage of atropin administered to cardiacs.

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**Protoplasmic Effects of Papaverin, Histamin and Other Drugs, in Relation to the Theory of Smooth Muscle Contraction.**

*Hoyt S. Hopkins, Am. J. Physiol., 61:551, Aug. 1, 1922.*

The author studied the effects of papaverin, benzyl alcohol, saponin, histamin, morphin, codein and apomorphin on such protozoa as (1)

Spirostomum teres, (2) Paramecium caudatum and (3) Astasia. It was found that papaverin causes an increase in the water content of the living animals, as shown by the increase in the size and number of their protoplasmic vacuoles. This leads to swelling of the body. Such animals, at death, cytolize rapidly. Benzyl alcohol gives rise to similar changes in the protoplasm, but causes little or no cytolysis. Saponin exercises a pronounced cytolytic effect on the cortical layer in certain protozoa, without influencing vacuolation, as does papaverin. Histamin produces constriction of the body in living protozoa, with reduction in size of the protoplasmic vacuoles. Morphin, codein and apomorphin exert stimulating and constrictor effects similar to those of histamin without influencing the rate of disintegration. The author says the effects of papaverin and benzyl alcohol, in so far as they lead to vacuolation and increased volume in protozoa, can be correlated with the depressor action of these drugs on smooth muscle cells; and those of histamin, and to a less extent of morphin, codein and apomorphin, with their stimulating effects on smooth muscle.

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**Physiologic and Chemicocolloidal Researches on the Mechanism of the Contracture of Striated Muscles Induced by Poisons. IV. The Mechanism of the Veratrin Action.**

*Otto Rieser and S. M. Neuschlosz, Arch. f. exper. Path. u. Pharmacol., Leipsic, 93:179, June 23, 1922.*

The characteristics of the veratrin action (concentration 1:20,000) were: No spontaneous contracture; on stimulation by individual induction discharges, slight rise of the contraction curve; prolongation of the fall of the curve; occurrence of a second rise (double summit). On repeated stimulation or prolonged poisoning, the muscle loses its ability to perform double contractions. The stronger the poisoning the greater the carrying power of the second elevation for weights. With intense poisoning (1:500) spontaneous contracture of the muscle sets in which, however, soon subsides. The muscle responds to individual stimuli without double contractions. In a concentrated solution the muscle loses its irritability.

In the experimental procedure, the frog's gastrocnemius was placed in a neutral veratrin hydrochlorid solution of different concentration and its lactacidogen content compared with that of a normal muscle (in Ringer's solution) after varying immersion. Results showed that neither large nor small doses (1:500-500,000) have any influence on the muscle's lactacidogen-phosphoric acid content. On the other hand, estimations of phosphoric acid in Ringer's solution surrounding the poisoned muscle showed that even very small veratrin doses arrest phosphoric acid elimination. This fact is related to veratrin double contraction. But if double contraction be abolished by rhythmic stimuli, phosphoric acid elimination again increases. The same parallelism between cessation of double contraction and increase of phosphoric acid elimination was observed by the authors with larger veratrin doses also. Emden observed that muscles in 7% cane-sugar solution lose their irritability, while phosphoric acid elimination increases. If the muscle were then placed in 70% cane-sugar solution in which veratrin



had been dissolved, the supervention of paralysis could be delayed and the increased elimination of phosphoric acid, caused by the sugar solution, arrested. All these phenomena are attributed by the authors to an altered state of the muscular colloids, which represents diminished permeability of the limiting layers, whereby the elimination of acid is arrested (acid congestion). On the strength of this hypothesis all aforementioned characteristics of the muscle's veratrin poisoning find an explanation, and those of double contraction and prolongation of the descending limb of the contraction curve in particular.

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### **The Effect of Quinidin on Striped Muscle.**

*J. G. Brody, J. A. M. A., 79:354, July 29, 1922.*

Experiments with frog's gastrocnemius or sartorius, immersed in dilute quinidin solutions, show variations from the corresponding normal muscle (immersed in unpoisoned Locke's solution): The height of contraction is diminished. With tetanizing currents, the peak of contraction is not so well sustained. The muscle ceases to respond to any stimulus much sooner than the unpoisoned muscle; load fatigues it more easily. About 10 stimulations a second cause a completely fused tetanic contraction in normal muscle; with the quinidin muscle fusion is usually incomplete and becomes less complete the more the muscle is fatigued or loaded. The quinidin muscle therefore responds intermittently to a tetanizing current.

These effects can be conceived as depression of the muscle, with slow recovery of excitability, and consequent failure to respond to rapid stimulation until the muscle has rested; there is, therefore, intermittent response to frequent stimulations, the rhythm of the contractions depending not on the frequency of the stimulation, but on the rate of recovery of the muscle. In consequence of the rest the contractions are strengthened. This seems to furnish a plausible explanation of the effect of quinidin on auricular fibrillation. Quinidin probably depresses the cardiac muscle, so that it cannot respond to the various stimuli that give rise to fibrillation, but only to a restricted number, thus giving opportunity for periods of rest.

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### **Constituents of Saffron. I. Picrocrocin.**

*E. Winterstein and T. Teleczky, Ztschr. f. physiol. Chem., Berlin, 120:141, June 1, 1922.*

Saffron is known as an excitant, emmenagogue, abortifacient and aphrodisiac, and has been little investigated so far. The pigment polychroit, or crocin, has not been prepared in the pure state. Adulterations of foods with saffron are innumerable. It is of importance, therefore, that saffron has at last been subjected to exact chemical investigation. By extraction of unadulterated fresh saffron with pure ether, a glucosid, picrocrocin or saffron bitter, may be prepared which is obtained, upon suitable purification, in the form of highly lustrous crystals several millimeters in length. Picrocrocin melts at 154-155° C. On hydrolysis it yields a ketone of the terpene series, formula  $C_{10}H_{14}O$ . This ketone is a colorless oil, possesses the characteristic saffron odor and boils at 93° C. at 14 mm. If the formula  $C_{10}H_{14}O$  ascribed to

crocetin, the colored component of the glucosidal red saffron pigment, is correct, a relationship in the chemical constitution of both compounds might be expected.

Up to the present time, only oxalic acid and a colorless compound have been obtained from crocetin by decomposition. It appears that on keeping, saffron picrocrocin is cleaved in small amount, possibly by ferments. The ketone thereby liberated then causes the appearance of the saffron odor. Pentoses, mannitose and galactose do not form on hydrolysis. Most probably a mixture of d-glucose and d-fructose is produced. Besides the ketone, whose yield amounts to 48%, sugar is formed to an extent of 54% calculated as d-glucose. The formula  $C_{10}H_{14}O$  is that of eucarvol and carvol. Picrocrocin shows little physiologic activity.

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**Physiologic and Chemicocolloidal Researches on the Mechanism of the Contracture of Striated Muscles Induced by Poisons. III. The Mechanism of Caffein Contracture.**

*Otto Rieser and S. M. Neuschlosz, Arch. f. exper. Path. u. Pharmacol., Leipsic, 93:163, June 23, 1922.*

Experiments were carried out with frogs' gastrocnemius to determine whether the action of caffein is attended by alteration of the muscle's lactacidogen content. If the muscle be immersed in a 1:1000 caffein sodiosalicylate solution, or in 0.5:1000 pure caffein, slow but constant shortening takes place, during which electric irritability diminishes until it ceases at the height of contracture; therewith commences the stage of invertible rigidity. With inconsiderable concentrations (pure caffein 1:8000) no spontaneous shortening occurs but the pedal of the individual contractions rises with rhythmic induction discharges during which the height of contraction diminishes. Upon cessation of irritation, the contracture persists.

With considerable caffein doses, which cause immediate contracture, lactacidogen-phosphoric acid invariably diminishes, during which free phosphoric acid is found to be increased. With small caffein doses the muscle's lactacidogen content is not altered initially, but if immediately afterward the muscle be stimulated electrically, it diminishes rapidly. As decomposition and formation of lactacidogen balance each other in the normal muscle, it must be assumed that caffein stops the restitution of lactacidogen. Phosphoric acid excretion into the surrounding Ringer's solution during the caffein action was determined. It was shown that phosphoric acid elimination rises during caffein contracture as against a normal control muscle, but smaller caffein amounts that do not cause contracture also increase phosphoric acid elimination. The authors refer this phenomenon to a physical alteration of the muscle colloids by caffein.

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**Concentration of Caffein in Rabbits' Blood and Urine after Parenteral Administration.**

*L. Loeb Farmer, Biochem. Ztschr., Berlin, 129:570, May 23, 1922.*

The concentration of caffein in rabbits' blood and urine was investigated with the aid of the biologic method of determining minute

amounts of caffein' according to Friedberger. The blood and urine samples were evaporated with added gypsum, the residue being dried in the desiccator over sulphuric acid, mixed with dried calcium sulphate, and extracted one hour with chloroform. To remove the last traces of chloroform with petroleum ether, the mixture was heated, the distillation residue dissolved in Ringer's solution and the muscle likewise examined in Ringer's solution. The method is a biologic one and is therefore subject to certain sources of error. The investigation of the parenterally injected caffein was carried out in blood, urine and feces by means of experiments at brief intervals. Intravenously injected caffein disappears partly in a few minutes from the rabbit's blood channel, but a considerable part can be detected in the blood for a long time. During the presence of this part of the caffein, excretion of caffein in the urine and diuresis take place. Subcutaneously injected caffein is also found in the blood and appears simultaneously in the urine.

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**Caffein Elimination in Urine After Tea and Coffee Ingestion in Man.**

*Okushima Kwanichiro, Biochem. Ztschr., Berlin, 129:563, May 23, 1922.*

Caffein elimination and its pharmacologic quantitative determination in the frog's skeletal muscle were investigated by Friedberg's method of extracting caffein from the urine. Experiments were also carried out on a Japanese and a European in order to ascertain whether the course of elimination differs in different races. The urine was tested hourly. The amount of caffein administered was 70-130 mg. With tea and coffee the course of elimination hardly differs. In the first hour after tea or coffee is taken only a slight amount of caffein is eliminated; in the second hour the amount is fairly large, and maximum elimination usually takes place in the third and fourth hours. Subsequently elimination diminishes gradually, but its total cessation is fairly slow. Caffein can still be detected in the urine after 10 to 11 hours. If liquids be taken during the experiment its elimination increases even 6 to 7 hours after the ingestion of tea or coffee. Contrary to Friedberg's results, this proves that caffein remains in the organism during this time and that it can be washed out by force of water. Friedberg has shown that the increased amount of urine favors the elimination of caffein in the urine. On the other hand, the kidneys are able, up to a certain degree, to eliminate a large amount of caffein, with intense perspiration, in spite of the reduced urine quantity, provided the resorbed caffein is present in the organism in sufficient amount. This is why the course of elimination is very similar in all cases in the first 5 hours, although in 2 cases the urine volumes were very small. As a matter of course the elimination of caffein is more or less retarded by such a condition. Individual differences in the course of the elimination are not demonstrable. Even with considerable difference in the sensitiveness of the brain to caffein, the elimination proceeds almost identically.

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**Elimination of Theobromin and Theobromin Diuresis.**

*Ludwig Günsburg, Biochem. Ztschr., Berlin, 129:549, May 23, 1922.*

Hitherto theobromin elimination in urine has been followed only summarily. Rost's method is very accurate but too inconvenient, Friedberg's inapplicable owing to the difficult solubility of theobromin. The following method was adopted. The urine having received additions of tartaric acid and gypsum was evaporated, extracted with chloroform, and the chloroform rendered anhydrous with ignited sodium sulphate. If the chloroform residue be treated with a little ammonia, theobromin passes into solution as easily soluble ammonia salt; excess ammonia is driven off by boiling. The residual theobromin is precipitated with silver nitrate, the filtrate mixed with iron-ammonia alum as indicator and titrated, after addition of nitric acid, with 0.02 n.  $\text{NH}_4(\text{CNS})$  solution until a permanent red coloration is obtained. Each cubic centimeter of the 0.02 n.  $\text{AgNO}_3$  solution corresponds to 3.60 mg. theobromin. Therefore what is involved is precipitation of the very weak ammoniacal solution of the chloroform residue with  $\text{AgNO}_3$  and titration of the  $\text{AgNO}_3$  loss according to Volhard.

Theobromin elimination in man followed by means of this method yields a characteristic curve with a rapid rise (maximum in the second or third hour after theobromin administration) and a moderately rapid fall which is essentially completed by the seventh hour. This curve is obtained also in the absence of diuresis. During maximum theobromin elimination the urine usually becomes alkaline or less acid. Theobromin diuresis may be materially limited by the simultaneous exhibition of alkali or increased by the simultaneous exhibition of acid. Chronic use of caffeine diminishes the sensitiveness to theobromin so that larger doses are needed to obtain the diuretic effect.

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**The Organotropic, Bacteriotropic and Leukocytotropic Actions of Certain Organic Chemicals.**

*Lloyd D. Felton and Katharine M. Dougherty, J. Exper. Med., 36:163, Aug. 1, 1922.*

The authors report on the toxicity for mice (organotropism), the bactericidal action on *Staphylococcus aureus* (bacteriotropism), and the antiphagocytic influence (leukocytotropism), of certain members of 7 groups of chemicals—triphenylmethane leuco-bases, triphenylmethane dyes, acridins, safranins, phenazins, quinons, and cinchonas.

The method finally adopted for the study of phagocytosis is given: 0.5 c.c. of leukocytes suspended in undiluted guinea-pig serum plus 0.5 c.c. of culture plus 0.5 c.c. of chemical were incubated for 15 minutes in a water-bath at  $37.5^\circ \text{C}$ . This simultaneous incubation of all constituents mixed together seemed more nearly to reproduce actual conditions of infection in the animal. Leukocytes were procured from the peritoneal cavity of a guinea-pig 15 hours after intraperitoneal

injection of a solution composed of 3% aleuronat, 6% starch, in 0.85% NaCl, by washing out the exudate with sterile 0.5% citrate in 0.85% NaCl. The cells were washed 3 times in sterile citrate solution before being used. Opsonin and complement were furnished by fresh guinea-pig serum and the organism employed as indicator of leukocytic activity was an 18 hour broth culture of *S. aureus*. Smears were made after incubation, and the preparations stained by Cross' method. The staphylococci found in 100 cells were counted and the counts averaged. Control counts were made from tubes containing leukocytes, serum and organisms, but no chemical. The bacteriocidal action of the drugs was determined in whole blood with 2 hour incubation period, by means of a technic previously described. All the chemicals tested possess a leukocytotropic action, as measured by decreased ability of leukocytes to ingest staphylococci. This action against the functional activity of the leukocyte is more pronounced than the organotropism or bacteriotropism (for staphylococcus).

Four aromatic cinchona compounds, hydroquinin chloracetylanilid hydrochlorid, dihydroquinin p-chloracetylaminophenol hydrochlorid, dihydroquinin m-chloracetylaminophenol hydrochlorid, dihydroquinin 4-chloracetylaminopyrocatechol hydrochlorid, and optochin are markedly antiphagocytic in their therapeutic dose. They possess a positive chemotactic action for leukocytes when injected into the peritoneal cavity of mice. With p-methoxymalachite green, ethyl violet chlorid, and diamino-acridin sulphate the condition was approached in which the concentration of a nonlethal dose for mice is staphylotropic and not leukocytotropic.

The only group of the 7 which definitely possessed an in vivo bacteriocidal action against pneumococcus is that of the cinchona derivatives. Certain members of other chemical groups studied, although bacteriocidal in very high dilution, had no certain effect when bacteria and drug were injected simultaneously into the peritoneal cavity of a mouse. It is assumed that the failure of these chemicals to exhibit a benign influence on systemic infection is due to their antiphagocytic property. To definitely settle this point and determine the *modus operandi* would be of practical importance in a rational development of chemotherapy.

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#### **Quantitative Researches on the Action of Thyroxin, Diiodotyrosin, Iodothyrim and Iodothyroglobulin.**

*Romeis, Klin. Wchnschr., Berlin, 1:1262, June 17, 1922.*

With these substances accelerated development, arrest of growth and increased dissimilation may be induced in the tadpole experiment. Thyroxin is most active and arrests growth even in a dilution of 1:100,000,000. Probably the substances derived from the thyroid gland having a specific action and described as iodine-free owe their effect to their thyroxin content. All forms of acceleration observed on tadpoles can be produced with thyroxin, but while its action is equally strong in young and old tadpoles, diiodotyrosin acts on young tadpoles in high dilution, on old tadpoles only in high concentration.



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**Evaluation of the Hormone of the Infundibulum of the Pituitary Gland in Terms of Histamin, with Experiments on the Action of Repeated Injections of the Hormone on the Blood Pressure.**

*John J. Abel and Charles A. Rouiller, J. Pharmacol. & Exper. Ther., 20:65, Aug., 1922.*

Repeated experiments have shown that it is possible to prepare an aqueous solution of the pressor and oxytocic principle of the pituitary gland, the organic matter of which is actually equal in oxytocic activity from 20-30 times its weight of the acid phosphate of histamin, or 12-18 times its weight of histamin hydrochlorid. It is estimated that when the active principle is freed entirely from the accompanying inert material, it will be found to be weight for weight 40-50 times more powerful in its action on the guinea-pig's uterus than histamin. This estimate is made on the assumption that the isolation of this unstable hormone as a chemical individual can be effected with the retention of its peculiar powers, as manifested in preparations described. In agreement with the writers' findings, it appears that the hypophysis of the ox, the posterior lobe of which weighs on the average 0.4 gm., does not contain more than 2 mg. of the oxytocic principle. The powerful solution with its extremely low content in organic matter, which is obtainable by the writers' method, exhibits all of the really characteristic physiologic activities of ordinary saline extracts of the infundibulum.

A first intravenous injection is always followed by a pure pressor vasomotor response; a later injection by a pronounced depressor vasomotor response, although the response to the later injection may be very slight. The actively secreting kidney of the rabbit responds to an injection by a diminished secretion or by an entire inhibition of the urinary flow.

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**The Action of Thallium.**

*A. Buschke and F. Jakobsohn, Deutsch. med. Wchnschr., Leipsic, 48:859, June 30, 1922.*

Buschke produced alopecia in animals by the administration of thallium salts, which effect probably occurs through the agency of the endocrine glands and of the vegetative nervous system. The authors therefore investigated the oligodynamic action of thallium. Experiments with various bacteria of the coli and dysentery groups and with staphylococci and streptococci demonstrated that metallic thallium, when laid on an Endo plate, produces a sterile space, 7-14 mm. wide, in the culture medium; this space is sharply defined, and is bounded by a zone of active growth. Experiments to determine the metallic activation of the walls of test-tubes have so far not given definite results. Thallium that has been brought to red heat and then cooled presents a decrease in oligodynamic action. After repeated use, a progressive decrease in its activity is noted (fatigability). No elective action in bacterial mixtures has been demonstrated.

To determine whether thallium exerts an ionic action upon the organism, isolated frog hearts were tested (Straub's cannulas) in

experiments based upon the fact that the action of poisons is increased or diminished by certain electrolytes, as potassium and calcium. Following the addition of small quantities of thallium (0.00003-0.00005 gm. thallium sulphate) a decrease in the contractions occurs, which may terminate in diastolic cessation of the beat in 10 or 15 minutes. The administration of calcium temporarily decreases considerably the effect of thallium or may temporarily check it entirely.

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**The Action of Tellurites on the Blood and the Hematopoietic Organs.**

*Angelina Levi, Haematologica, Naples, 3:343, July, 1922.*

The author's researches have borne out the conclusions already arrived at by other investigators that sodium tellurite is one of the most violent of hemolytic poisons and that the toxic or fatal action of tellurites may be attributed exclusively to the great affinity that exists between the red corpuscles and these salts. The microscopic lesions in the organs observed in tellurite poisoning are secondary to intense anemia, hemoglobinemia, etc. No profound organic lesions are observed.

Attention is drawn to the absence of icterus in these forms of poisoning. From the intense hemolysis and the slight hepatic lesions he is inclined to believe that there does not exist any real hematogenic icterus, as other writers affirm. When relatively large doses of tellurite are injected, a part of the tellurium is eliminated by the urine in a colloidal state.

These studies also bring out the analogy between chronic tellurite poisoning and pernicious anemia (high hemoglobin index).

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(1c—73)

(1c—73)

**Further Observations of the Pharmacology of Benzyl Compounds. II.**

*Carl Nielsen and John A. Higgins, J. Lab. & Clin. Med., 7:579, July, 1922.*

Pharmacologic investigations were undertaken to establish the relative efficiency of various benzyl esters and other benzyl compounds as intestinal relaxants. Observations previously recorded suggest a correlation of rate of benzyl hydrolysis and smooth muscle relaxant property in the cases of simple benzyl esters. Exceptions to this rule are benzyl salicylate and benzyl acetylsalicylate, which produce relaxation of the intestine, in situ, greater than expected from their benzyl content and rate of benzyl hydrolysis. Following the same technic as with the esters, the duodenum of the cat was injected with various other salicylates, as well as acetylsalicylic acid, to determine whether the relatively powerful relaxant action on smooth muscle of these two benzyl esters may be ascribed in part to their acid radical. These solutions were employed: 0.2 c.c. of a 10% solution of acetylsalicylic acid in 0.1 n. alcoholic sodium hydroxid, 1 c.c. of 10% sodium salicylate, 0.1 c.c. methyl salicylate and methyl alcohol to control the methyl element

in the methyl salicylate. None of these acids alone possesses any striking power to relax the intestine.

Benzyl salicylate, when treated with alcoholic potassium hydroxid, *in vitro*, has the lowest rate of hydrolysis of all the benzyl esters under investigation. The rate of hydrolysis of the benzyl group in benzyl acetylsalicylate does not exceed that of the salicylate. The experimental evidence indicates that the relatively potent relaxant action of these two benzyl esters, as contrasted with benzyl esters of a much higher rate of hydrolysis, is not the ensemble of their molecular constituents, but rather a more powerful one possessed by the intact molecules.

Investigations of benzyl esters of higher melting points (solid above room temperature) were carried out usually with the Trendelenburg method. The benzyl esters were dissolved in sweet almond oil in such amounts that the various solutions used for injection contained the same proportion of benzyl radical. The esters so studied were benzyl stearate and fumarate, benzyl para-amino-benzoate, benzyl acetate, succinate and cinnamate. Here again, the higher the rate of hydrolysis the greater was the relaxant action. Thus, benzyl fumarate was more efficient than benzyl succinate, particularly with regard to initial action; the succinate is more efficient than the stearate, the acetate more powerful than the cinnamate, which in turn is more potent than the benzoate. Various benzyl compounds other than benzyl esters, such as benzyl phenolate, benzyl ethyl ether, monobenzyl barbituric acid and benzaldehyde, were also found to possess smooth muscle relaxing properties.

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(1c—74)

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#### **Disinfectant Efficacy of Dyestuffs and Metals in Combination.**

*Hans Langer, Ztschr. f. d. ges. exper. Med., Berlin, 28:45, June 7, 1922.*

The efficacy of dyestuffs for internal disinfection has recently been enhanced by combination with various metals, particularly silver. The rationale of the combination is based on the assumption that the combined action must be stronger than that of the dyestuffs alone. Any attempt to explain the mechanism of such increased efficacy leads first of all to the supposition that nonspecific factors—elements concerned with stimulation or irritation—participate in bringing about the good results obtained. Such supposition is strengthened by the fact that the combinations are often made with colloidal metal preparations, and thus justify the attribution of their effects to some nonspecific factor. Some have gone so far as to ascribe these effects not to the colloidal metal itself, but to the protective colloid which is added merely to insure stability of the preparation. But this angle of the problem affects little the more common dyestuff and metallic combinations, since they contain no protective colloid. On the other hand, it is of the greatest significance to notice that these combinations, even when the metal added is not at all in colloidal form, will display markedly increased efficacy even *in vitro*. The phenomenon observed is therefore one of true increase in the actual disinfecting property of the preparation.

The author has instituted experiments concerning the ability of

certain substances, added to variously diluted solutions of flavicid, to inhibit the growth and development of *Staphylococcus aureus*. He used hydrochloric acid, cadmium chlorid, ferric chlorid, silver nitrate, ammonium nitrate, zinc sulphate, copper sulphate, sodium tellurite, and thymol. It was evident that the disinfecting substance (colloidal silver, thymol, etc.) was ineffective, whereas the metallic salts were uniformly active. The occurrence of a summation of stimuli is therefore inadmissible as an explanation of the increased antiseptic properties of the mixtures. A chemical transformation is likewise improbable, since various experiments with combination mixtures (such as aeridium plus silver nitrate) in progressively increasing dilutions—in spite of the greater ionization thus brought about—did not result in any increase in antiseptic properties.

Langer suggests that the metallic salt causes a greater diffusibility of the dyestuffs in solution and leads thus to a more pronounced efficacy of the latter; at the same time there is a union of metal with dye particles and therefore also with bacteria. The altered diffusibility of the dyestuffs through the addition of metallic salts acts as a method of fixation of the metal particles.

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(1c—75)

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**An Interference Phenomenon in the Action of Chemotherapeutic Substances in Experimental Trypanosome Infections.**

*C. H. Browning and R. Gulbransen, J. Path. & Bacteriol., Edinburgh, 25:395, July, 1922.*

The observations here described demonstrate the effect of one substance (parafuchsin) when present in the tissues interfering with the therapeutic action of another (amino-acridin compound) in the case of infections in mice with a strain of nagana trypanosomes which had been rendered resistant to the former (parafuchsin). In the authors' experiments resistance to the chemotherapeutic agent was conferred in the usual fashion by prolonged treatment of infected animals with amounts of parafuchsin insufficient to cause complete sterilization. For this purpose the parafuchsin is usually incorporated in the animals' food. The resistance is shown by the fact that when normally fed mice and animals fed with parafuchsin for some days prior to inoculation, so that they are "saturated" with the dye, are both inoculated with the resistant strain, the infection "takes" equally in each series, and the parasites increase progressively, causing death in 2-3 days. On the other hand, if 2 similar series be inoculated with the original strain, the majority of the mice fed with parafuchsin will in most cases fail to become infected and those which do become infected will probably show no trypanosomes in the blood for long periods when feeding with parafuchsin is continued.

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(1c—76)

(1c—76)

**New Method for Demonstrating Drugs of the Veronal Group.**

*Heinrich Handorf, Ztschr. f. d. ges. exper. Med., Berlin, 28:56, June 7, 1922.*

The enormous number of different drugs lately put on the market, with the correspondingly increased possibilities of fatal poisoning, have

in quick succession added to the problems and increased the difficulties of toxicology. This applies as well to the present situation with respect to veronal and its allied preparations and derivatives. Cases of poisoning with this class of drugs form an alarmingly large proportion of the intoxications crowding the hospitals and dispensaries. Since differential diagnosis at the bedside between the various narcotics and hypnotics is often physically impossible, it becomes necessary to devise some method or methods for roundabout identification of the responsible toxic substance, methods totally independent of clinical signs or symptoms.

The author's own method consists in the formation of the murexid of the alloxan nucleus of veronal. The test may be performed as follows: 100 c.c. urine are acidified with acetic acid and shaken after mixture with ethyl acetate or ether. The latter is then evaporated off. The residue is boiled with hydrogen peroxid (to which ammonium chlorid has previously been added), then further heated over a wire netting. In positive cases there appears the yellow-red color and all other characteristics of the murexid test. If it is a question of differentiating between veronal, proponal, medinal and luminal, the extract is divided into 3 portions, the residues of which are treated with ammonium chlorid, sodium chlorid and barium chlorid. Veronal gives a positive reaction in the presence of sodium chlorid as well as of ammonium chlorid; the same is true of proponal, except that at 100° C. the reaction is much slower; medinal is positive with ammonium chlorid but negative with sodium chlorid, the former test being complete and characteristic only at very high temperatures; luminal gives a negative test with barium chlorid.

In reviewing his findings the author points out that his method for demonstrating the presence of veronal and allied substances does not require actual physical isolation of these drugs, but consists rather in a gross reaction of the patient's urine (precipitation) without previous preparation, using only alcohol to avoid emulsification, and obtaining in this manner a solution containing veronal. Whether such solution contains other chemical bodies, and what the exact character of these bodies may be, is a matter of no importance. The test, in spite of its apparent multiplicity of steps, may be completed in a very short time and with very little effort. All the by-products obtained by the other distillation methods and which caused all the difficulties and confusion in the way of isolation of the actual veronal and allied compounds, are completely obviated in this test. The appearance of murexid is so striking that it permits of correct identification of a toxic substance in even the minutest quantity and from the most unfavorable specimens of urine, where any attempt at actual isolation of the drug would of necessity be unsuccessful. Any specimen of urine containing a quantity of veronal or allied body insufficient even to suggest recourse to physical isolation of the drug, is susceptible of correct diagnosis and positive demonstration of the presence of the toxic product by the test here suggested. One of the cases brought before the author was that of an individual who had received a single dose of veronal of 0.5 gm. and was brought for examination 40 hours later, during which time he had passed 2000 c.c. urine that had not been preserved for examination. The test was positive.

Furthermore, the actual physical demonstration of veronal in the  
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urine has no clinical significance of moment, because (1) in different individuals there is a different rate of excretion of the same dose of the drug; (2) in most clinical cases it is sufficient for the clinical attendant to know that the quantity of veronal found is such as to be held responsible for the condition of the patient, and that it is not an accidental discovery, as where the drug has been taken only in therapeutic dose before or after some other toxic substance. This differentiation, however, may now be accomplished by a mere glance at the residue left after evaporation of the ether, as well as by the degree of intensity of the murexid test.

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(1c—77)

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**The Active Principle of Korean Ginseng.**

*K. Abe and I. Saito, Japan Med. World, Tokio, 2:166, June 15, 1922.*

While ginseng has been frequently studied chemically, its active principle has not yet been definitely determined, possibly because the drug, though used for a great variety of ailments, does not have a specific curative effect upon any of them. Preliminary studies have established the fact that the drug produces an effect upon carbohydrate metabolism.

In the present experiment, dried ginseng was extracted in petroleum ether, then in warm ether, and finally in alcohol. These 3 extracts were examined for their action upon sugar. I. The petroleum ether extract was soluble in water; a 25% aqueous solution of it slightly increased the blood sugar in rabbits. II. The ether extract, insoluble in water but soluble in glycerin, produced similar results as solution I. Control experiments made with glycerin only showed a less marked increase. III. The alcoholic extract, also water soluble, produced a slight diminution of the blood sugar in rabbits. The experiment included the study of the effect of the alcoholic extract upon an artificial adrenalin hyperglycemia. It was found that solution III, when injected a short while before an adrenalin solution, prevented the hyperglycemia ordinarily produced by adrenalin. Thus, the alcoholic extract contains the active principle of the drug. The authors corroborated the tests of Kondo and Tanaka, which established the chemical nature of this alcoholic extract as a glucoside.

**TOXICOLOGY**

(1c—78)

(1c—78)

**Acute Arsenical Poisoning.**

*Sir William Henry Willcox, Brit. M. J., London, 3212:118, July 22, 1922.*

Arsenious oxid is most commonly used for criminal purposes—a white inodorous powder, almost tasteless. Commercial preparations (weed killer, wood preservatives, fruit sprayer) frequently cause fatal arsenic poisoning; medicinal preparations cause poisoning when taken in excessive doses. Though usually described as an irritant, arsenic is a powerful tissue poison; the toxic effect on important organs (heart,

kidneys, and liver), causes the fatal result. Symptoms are variable, depending on condition of the stomach at time of dosage, whether food is taken simultaneously, and whether arsenic is in solution or solid state. Vomiting, diarrhea, throat burning, thirst, and leg cramp have been noticed. A weak and rapid pulse is an early and constant symptom. Arsenic is a direct liver poison, resulting in fatty degeneration, diminished hepatic function, and a jaundiced appearance in protracted cases. Kidney function is impaired, shown by diminution or even suppression of excretion, and presence of albuminuria. Nervous symptoms do not follow a single dose; multiple neuritis may follow a large dose, and usually follows repeated doses. A single dose of 2 gr. arsenious oxid is usually accepted as a possible fatal dose.

In postmortem examination only reliable methods should be employed in the analysis of organs. The Reinsch test, and the electrolytic Marsh-Berzelius test are dependable. In toxicologic work reliance should not be placed on a single method; if arsenic is found by one, presence should be confirmed by the other. Vomit and feces will contain arsenic in amount depending on quantity taken; absorbed arsenic will be found in the blood and serous exudations. After prolonged administration some becomes deposited in skin, hair, and nails. Tables show the excretion and distribution of arsenic in the body in fatal cases. In poisoning by arsenobenzol derivatives, the effects on the organs produce the fatal symptoms; the liver suffers most. Symptoms of acute salvarsan poisoning exactly simulate those of icterus gravis, and are, in the author's opinion, due to auto-intoxication from defective liver function, consequent on the poison action on the liver cells.

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(1c—79)

(1c—79)

#### **Calcium Chlorid in Cocain Poisoning.**

*F. Fabry, Münch. med. Wchnschr., 69:969, June 30, 1922.*

In a case of very severe cocain poisoning after tonsillectomy, the intravenous injection of 10% calcium chlorid solution (5 to 10 c.c. within just as many minutes), as advised by Karl Meyer, had an immediate and most excellent result. The use of calcium chlorid as an antidote for cocain poisoning is suggested by the consideration that this remedy acts as an excitant of the respiratory center and in this way counteracts the paralyzing effect of the cocain.

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(1c—80)

(1c—80)

#### **Blood Picture and Blood Crisis in Experimental Lead Poisoning.**

*Hans Rauch, Ztschr. f. d. ges. exper. Med., Berlin, 28:50, June 7, 1922.*

Rabbits were exposed for weeks to a lead-laden atmosphere. Changes in the red cells of these animals became noticeable on the fourth day—normoblasts, basophilic erythrocytes with basophilic granules, red cells with Howell-Jolly bodies, degenerated red cell nuclei and, after the eighth day, freely floating expelled red cell nuclei. There was also an increase in platelets. The white-cell count was little, if at all, changed, absolutely; but there was a marked relative lymphocytosis.

The picture is therefore one of blood crisis. This is further emphasized by the marked decrease in red-cell count (to one-half the normal); the count increased after the fourteenth day and, following elimination of the lead from the atmosphere, returned to normal. The marked fall in red cells after exposure to lead inhalation causes the appearance in the circulation of immature red cells (blood crisis) and even these, on continued exposure, degenerate later.

The author assumes that the basophilic stippling represents products of degeneration within the erythrocytes; however, such evidences of degeneration were noticeable only in the poorly resistant immature red cells. This points to a possible simultaneous regeneration of blood-cells. These newly formed elements also degenerate following exposure to the same deleterious influences. For a like reason there appear evidences of degeneration also in the leukocytes, explainable as the result of either physicochemic or toxico-infective processes, neither of which a living being can long escape.

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(1c—81)

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### **Corrosive Sublimate Poisoning.**

*Ch. Achard, Paris méd., 12: 33, July 8, 1922.*

In a case of corrosive sublimate poisoning with death on the tenth day, the main symptoms were painful hematemesis; bloody diarrhea; stomatitis with a tendency to necrosis; anuria during the first 4 days, after which the secretion of urine gradually increased; moderate albuminuria; general weakness and anxiety; no fever, no cardiac disorder and no tendency to hemorrhage; coagulation time normal; bleeding time slightly increased. Blood pressure was at first 9.5-5.5, then rose to 21-10 on the fifth day and went down to 14-6 before death.

In a review of the pathology of corrosive sublimate poisoning, Achard lays special stress on the question of azotemia. In this case there were 1.95 gm. urea per liter in the blood on the first day, and 7.02 gm. on the seventh. Even when the secretion of urine is reestablished the quantity of urea eliminated by the kidneys is usually insufficient and azotemia continues to increase. In favorable cases it decreases only slowly. It is doubtful whether retention of urea alone causes death, for this substance is not very toxic. Of late, residual or non-ureic nitrogen has been especially incriminated in uremia. There are cases, however, where the quantity of nonureic nitrogen present in the blood seems too small to produce death, as in a patient of the author's who had 6.67 gm. urea and only 0.18 gm. residual nitrogen per liter of blood. In another case, however, 0.89 gm. residual nitrogen were found. In short, death may occur with a large quantity of either urea or residual nitrogen, associated with a moderate or small quantity of the other substance, but other nonnitrogenous bodies are perhaps also responsible for the toxic phenomena resulting from urinary retention. Although uremia plays a very important rôle in fatal cases of corrosive sublimate poisoning, the symptoms naturally differ from those produced by various other forms of anuria having a different cause. Once lesions have developed the treatment can only be of a palliative nature. Injections of hypertonic glucose solutions are advised because they help in

reestablishing at least the excretion of water, so that edema cannot form, and they bring a small quantity of food to the organism.

(1c—82)

(1c—82)

**Phenol and Cresol Poisoning.**

*Raphael Isaacs, Ohio State M. J., 18:558, Aug. 1, 1922.*

In phenol poisoning, simple lavage, with 5% sodium bicarbonate solution, 3-6 qt., is as effective as many of the long list of drugs that have been used. Magnesium sulphate, 60-120 c.c. of a 50% solution, is left in the stomach, mainly for its cathartic action, although it frequently produces emesis. In comatose cases, the most prompt results are obtained if a salt solution—normal saline, or magnesium sulphate 2%, or preferably a sodium chlorid (1.4%) and sodium carbonate (.37%) solution, 500-1000 c.c.—is given intravenously. Sodium bicarbonate forms the most convenient wash, whether as first aid or later. Petrolatum may be applied to the skin in the later stages. If alcohol is available, it is of use in washing off the skin, but one should also consider the effects of the denaturalizing agent which it may contain.

The patient is kept in bed until signs of hemorrhage and renal irritation have disappeared. Pain in the gastro-intestinal tract may be relieved with orthoform, 1 gm., but it may be necessary to use morphin. A fluid or light diet may be given. If a stimulant is necessary, caffeine-sodium benzoate hypodermically is effective. Calcium lactate may be given, especially if there is bleeding. Enough alkali, soda bicarbonate and soda citrate is given by mouth to keep the urine just alkaline to methyl red. Under this treatment evidence of renal irritation seems to clear up rapidly. It is well not to pass the stomach tube if the patient is unconscious, certainly not if his reflexes are dulled. In the author's series, the average duration of the period of hospital observation for those who had taken some form of alcohol previous to drinking the phenol was 4.2 days, while the stay of the others was 7.8 days. The average duration of hospital observation of the cases treated simply with the sodium bicarbonate treatment was 4 days, while the average stay for the more complicated treatment was 6.8 days. Artificial heat is used when the temperature is low.

In lysol poisoning, repeated confirmation in many cases has shown that a simple lavage, either with the stomach tube or induced vomiting, using 5% solution sodium bicarbonate, is quite effective. Magnesium sulphate may be used following the lavage to induce catharsis. In cases of severe collapse, caffeine-sodiumbenzoate hypodermically may be used, but the quickest and safest method is to give a saline solution intravenously, as in the case of phenol poisoning, 500-1000 c.c., repeating in 12 hours if necessary. The skin and mucous membrane burns may be washed with sodium bicarbonate solution (2-5%). If very edematous, magnesium sulphate (50% solution) may be used on the mucous membranes. Orthoform as a spray or 1 gm. internally may be used to relieve pain. For burns in the eyes, olive oil irrigations have been used. Petrolatum may be applied to the skin and lips. A liquid or soft diet may be given until the danger of hemorrhages is past. The average duration of hospital observation was 4.3 days. So far, no strictures or symptoms of scar formation in the gastro-intestinal tract have developed in the author's series, after the lapse of 1-5 years.

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**On Rhododendron Poisoning.**

*S. W. Hardikar, J. Pharmacol. & Exper. Ther., 20:16, Aug., 1922.*

Andromedotoxin, the active principle of the rhododendron, acted upon the terminations of the vagus, which it first stimulated and then paralyzed. This explained some of its most prominent effects, which were: (1) an alternation of inhibition of respiration for short periods, and respiratory movements; (2) slowing of the respiratory rhythm; (3) dyspnea of the asthmatic type, due partly to stimulation of afferent fibers and partly to spasm of the bronchial muscle from stimulation of its motor nerve, the vagus; (4) increase of bronchial secretion; (5) slowing of the heart and fall of blood pressure followed by acceleration and rise of pressure; (6) repeated evacuation of the bowels; (7) paralysis of the motor nerve ends in striped muscle. While the paralysis was developing, the muscle and nerve were more easily fatigued, but regained their excitability after a period of rest. In a stronger concentration the poison also affected the muscle substance itself, which thus lost its excitability permanently. The manifestation of this fatigue was seen best and earliest in the nerves and muscles which had to be constantly in action, viz., the phrenics and diaphragm. With very large doses death supervened rapidly and was due to a direct action upon the heart, the ventricles being arrested in diastole or partial systole. With smaller doses, death was due to failure of the respiration through a paralysis of the phrenics and often of the diaphragmatic muscle also.

There was a narcotic action upon the higher centers in the brain. The spinal cord was not affected. It produced a condition of arrhythmia in the heart dependent upon a direct depressant action upon the conducting tissue between the auricle and ventricle leading to heart-block, or upon the excitability of the ventricle itself. The period required for diastolic relaxation of the ventricle was increased and the diastole was incomplete. The perfused frog heart was arrested with the ventricle as well as the auricle in diastole, while in a frog injected with a fatal dose, the ventricle was arrested in total or partial systole with the auricles distended. The perfused mammalian heart was arrested in systole of the ventricles, but in death of an animal injected with the poison, the right side is distended and left empty or in partial systole. The poison had a slight vasoconstrictor effect of peripheral origin upon the blood-vessels. Involuntary muscle which was not supplied by the vagus was not affected. The increased secretion of saliva is probably only the first stage of the emetic action, and was not due to a specific effect upon the salivary glands or their secretory nerves. At least a third of the poison injected hypodermically left the body unchanged in the urine.

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**Saccharin Poisoning.**

*Pankraz Heilmann, Münch. med. Wchnschr., 69:969, June 30, 1922.*

A 9 year old boy took 200 saccharin tablets of 0.07 gm. each, containing in all 3.5 gm. refined saccharin. That night he suffered slight gastric pains; the next morning there was a severe disturbance of con-



sciousness of short duration and of a delirious character with auditory hallucinations and motor unrest, associated with an urticaria with bleb formation; 10 days later there were erythematous stripes and spots. The urticaria must be considered as a true internal urticaria in which the vessel nerves of the skin are overstimulated by irritating substances which reach there in the circulating lymph stream.

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(1c—85)

(1c—85)

**Generalized Megalokaryocytic Reaction to Saponin Poisoning.**

*J. Firket and E. S. Campos, Bull. Johns Hopkins Hosp., 33:271, Aug., 1922.*

The injection of saponin into the blood stream of rabbits produces hyperplasia of the bone-marrow with diffuse or focal hemorrhages. There is not a true aplasia. As the function of the bone-marrow is impaired by the hemorrhages and their effects, there occurs a vicarious myeloid reaction in the spleen, liver, and other organs. The new-grown myeloid tissue shows not only an unusually large number of nucleated red cells but principally the reaction produces megalokaryocytes; these are not all of the same appearance, and it is a question whether they are different strains of cells or different stages of the same type of cell. Saponin causes hemolysis of the red cells. Intravenous injections of this substance do not alter the resistance of the red cells to the drug. Splenectomy does not alter the resistance of the erythrocytes to saponin, although the resistance to hypotonic salt solution is altered by removal of the spleen, as shown by Pearce and others.

In addition to its hemolytic action, saponin is a highly destructive agent for blood platelets. This fact was first ascertained in experiments done on the living animal, and confirmed by test upon the blood in vitro mixed with saponin. This latter experiment completely confirms Bunting's discovery of the effect of saponin upon platelets, and rules out a suggested possibility that the drug perhaps merely drives the blood platelets out of the peripheral blood into some obscure resting place. It is not easy to understand why saponin should damage the capillaries of bone-marrow and nowhere else. An interesting find was that after removal of the spleen the myeloid reaction occurred also in the lymph-nodes.

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(1c—86)

**Suprarenin Poisoning.**

*F. Kleeblatt, Münch. med. Wchnschr., 69:970, June 30, 1922.*

Through a druggist's mistake, a female patient received 8 c.c. of a 1% novocain solution in a suprarenin solution (1:1000), totaling 8 mg. suprarenin, for neuralgia. Symptoms of poisoning developed immediately, namely agonizing headache, at first a hard pulse, then, after vomiting, collapse with an almost impalpable pulse and a sense of oppression. Recovery followed soon, but there were still pressure on the chest and headache for 2 days longer. The marked effect of a dose, in itself not large enough to cause such severe symptoms, was no doubt due to the fact that the solution was concentrated.

(1c—87)

(1c—87)

**Intoxications Caused by Tetrachlorethane.**

*Frois, Bull. Acad. de méd., Paris, 88:40, July 11, 1922.*

This substance ( $C_2H_2Cl_4$ ) is a valuable solvent used in various industries, particularly to dissolve cellulose acetate. It is very toxic and has given rise to several fatal accidents. Three cases of this nature have recently come under the author's notice, which occurred among women employed in an artificial pearl factory, where a tetrachlorethane varnish was used. Intoxication first produces headaches, dizziness and vomiting. Relapses are more severe than the first intoxication and are manifested by jaundice. The liver and kidneys are the organs principally affected. There is no alteration of the blood. Ventilation is not sufficient to prevent workmen from absorbing tetrachlorethane vapors. These should be sucked down by ventilators at the points where they are produced and evacuated outside or condensed and collected.

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**Experimental Researches on the Action of Tetrodotoxin (Fugu Poison).**

*K. Iwakawa and S. Kimura, Arch. f. exper. Path. u. Pharmacol., Leipsic, 93:305, June 23, 1922.*

Tetrodons (globe-fish), named fugu in Japanese, contain a poison, especially in the ovary. From the ovaries of poisonous tetrodon species, a poison was isolated which is easily soluble in water but insoluble in alcohol. The poison leads to atonic paralysis of the whole body similarly to curare. The lethal dose for the frog is 0.002-0.007 gm. per kilo weight. Death takes place from arrest of respiration. The lethal dose for mice is 0.002 gm.; for rabbits, 0.0015 gm. per kilo. Spinal paralysis sets in later than that of peripheral nerves and during it the muscles' irritability remains intact. Nor is a narcotic action on the brain detectable as respiration and corneal reflex are abolished.

In decapitated frogs, an anesthetizing cocain-like action of the poison is demonstrable by acid irritation of the legs. In the frog, miosis from tetrodotoxin depends on a central effect the same as the antipyretic influence on heat puncture hyperthermia. Arrest of respiration is due to: (1) central paralysis of the respiration center; (2) paralysis of the phrenic and other nerves of the respiratory musculature. Which of the 2 components first becomes active depends materially on dosage and manner of application. With slow resorption of the poison and small doses, paralysis of the respiration center sets in first (subcutaneous injection), while in intravenous application, paralysis of the phrenic nerve precedes arrest of respiration. It may be shown on mice and rabbits that adrenalin alone, or its combination with pituitrin, alleviates poisoning symptoms, particularly those of arrest of respiration and blood-sugar decrease, or may abolish the tetrodotoxin effect. Thus, a rabbit may recover from poisoning by as much as 2.6 mg. tetrodotoxin per kilo body weight if 0.2-0.3 c.c. adrenalin and pituitrin are injected. Adrenalin and pituitrin are therefore advocated as antidotes in globe-fish poisoning.

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**Subcutaneous Uranium Poisoning in Rabbits.**

*Bernhard Bartfeld, Biochem. Ztschr., Berlin, 129:534, May 23, 1922.*

Uranium intoxication in animals shows albuminuria, cylindruria, hematuria and glycosuria. Death usually supervenes on the fifth day under conditions of anuresis. A comparison of blood and urine analyses ought to reveal to what extent the nature of the process consists in a general affection, or in nephritis. For this purpose serial analyses were undertaken to show what alterations take place in the blood in the course of Pohl's disease, whether these appear together with or subsequent to alterations of the urine, and how the blood and urine results are related to each other quantitatively. According to the investigations, Pohl's subacute nephritis is a disturbance of metabolism, with strong accumulation of nitrogenous waste in the blood, while the kidney eliminates undiminished, and generally increased, amounts of nitrogen. The kidneys are not affected. This disease, which frequently persists for many weeks, can be induced by a single injection of 0.35 mg. uranium nitrate. The experiments were carried out on rabbits. The sodium chlorid value of the blood rose a few days before death. The experiments do not furnish an explanation of the nature of the disease. It is conjectured, on the strength of Hamburger's and Brinkmann's researches, that uranium glycosuria is to be regarded as an effect of the radio-activity of uranium. Possibly, also, the catalytic action of uranium, familiar in chemical reactions, may play a part in the origin of the disease. No analogue to the disease picture described exists so far in human pathology. The experiments render it doubtful whether increased residual nitrogen in the blood of kidney patients is always to be attributed only to retention by the kidney. Possibly individuals may also be attacked by a disease which appears clinically as nephritis but is in reality a profound metabolic disturbance of the entire organism, leading to increased formation of nitrogenous products in the blood.

**1d. BACTERIOLOGY AND PARASITOLOGY**

(1d—93)

(1d—93)

**The Importance of a Training in Chemistry to the Bacteriologist.**

*J. Martin Beattie, J. State Med., London, 30:300, July, 1922.*

The achievements accomplished in the field of bacteriology have largely been due to the credit of medical bacteriologists. But to-day there are questions which the bacteriologist needs chemistry to explain. Beattie discusses some well known problems of bacteriology, such as a correct chemical constitution of media, the errors occurring in the Gram reaction, the Wasserman, etc., which depend on chemistry to solve. Beattie believes that there are many other facts which one could use to show the value of a thorough training in chemistry by every bacteriologist, or appointment to every laboratory of a trained chemist who would work in close association with the bacteriologist.

(1d—94)

(1d—94)

**A Lumbar Puncture Needle for Bacteriologic Work.**

*H. R. Dean, J. Path. & Bacteriol., Edinburgh, 25:398, July, 1922.*

This needle was designed to avoid contamination of cerebrospinal fluid by the hands of the operator. The stilet is mounted in a guard which, when the stilet is in the cannula, completely covers and protects the aperture of the cannula from contamination. After sterilization the needle with the stilet still in position is inserted in the usual manner. When the point of the needle has entered the theca, the stilet is withdrawn and the fluid is allowed to escape through the aperture which, until the time when the stilet is removed, has been protected by the guard.

(1d—95)

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**The Staining of Spores.**

*A. Alessandrini, Ann. d'igiene, Rome, 32:362, May, 1922.*

There is a common notion concerning bacteriologic technic that spores fix with difficulty the staining substances, but once colored resist well the action of decoloring agents, which permits their differentiation from the microbic bodies. The writer gives a procedure that produces extremely good results, above all constant, and which offers economy of manipulation over other methods, in some of which the reagents, such as platinum chlorid, are very expensive and not always obtainable.

The technic is thus outlined: (1) Spread the material in the usual manner and allow it to dry. (2) Fix the preparation by passing it, as usual, 3 or 4 times through the flame. (3) Use Ziehl's solution, heating it first to the point of producing vapor for 2 minutes. Allow it to cool for 15-20 minutes and then wash with plenty of water. (4) Treat with a watery solution, 5%, of sodium sulphate to the point of decoloration. According to the thickness of the material examined this time will vary, but even a markedly prolonged immersion (1 hour or more) in the solution will do no damage. Wash thoroughly with water. (5) Stain for  $\frac{1}{2}$  to 1 minute with a watery solution of methylene-blue or malachite green, 1 or 2%.

This extremely simple method gives excellent results and may even be used for histologic sections. It is not necessary to precede the staining with the Ziehl by any special treatment because the spores take the color equally well, overcoming the resistance of the membrane with the usual fixation. This method, moreover, is shown to be superior to all methods previously described by the fact that it is equally applicable to all the different varieties of spore-bearing bacilli, while the other methods are insufficient because of the difficulty of generalizing, some procedures that act well for certain spore-bearing microbes not being efficacious for others.

(1d—96)

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**Nutritional Factors in the Growth of Yeasts and Bacteria.**

**I. Vitamins.**

*Louis Freedman and Casimir Funk, J. Metab. Research, 1:457, April, 1922.*

The authors sought to remove existing uncertainties regarding the identity of the substance that promotes growth of yeast cells with

that of vitamin B and its relation to the bacterial growth-stimulating substance. A strain of hemolytic streptococcus was employed for the experiments. The culture medium was prepared from fresh, finely chopped, fat-free beef heart by boiling with distilled water; the infusion was strained, filtered and boiled with norit charcoal, the decolorized liquid filtered and mixed with a glucose-salt solution, the mixture boiled, filtered, adjusted to a pH = 7.4 and sterilized. The effects of this and other mediums on growth of streptococci and yeast cells were studied. Further, autolyzed yeast and beef-heart infusions were shaken with varying amounts of fullers' earth and norit and in a few cases with Lloyd's reagent, being extracted thereafter from these adsorbents with baryta and acetic acid respectively.

Experimental results are recorded in tables. Possibly the nature and reactions of the mediums have an important bearing on these adsorption experiments. The theory is advanced that inhibiting substances may also be present so that a solution, inactive previous to adsorption, may become active thereafter. The results show the substances extracted from beef-heart infusions, peptone and autolyzed yeast which promote growth of yeast cells and hemolytic bacteria, to belong to the vitamin B class, but are not identical with vitamin B though their activity and properties are similar. The authors conclude that they are identical either with the vitamin D described by Funk and Dubin or so similar to the same that only their isolation, purification and complete analysis will enable them to be differentiated. Beef and beef-heart infusions also contain another substance necessary for growth of hemolytic bacteria which is assumed to be associated with hemoglobin.

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### **Nutritional Factors in the Growth of Yeasts and Bacteria.**

#### **II. Protein Hydrolysates.**

*Louis Freedman and Casimir Funk, J. Metab. Research, 1:469, April, 1922.*

Proteins and protein hydrolysates are employed for enriching bacterial culture mediums but bacterial growth has rarely been shown to be definitely attributable to them. In most cases vitamins were also present. Some authors suggested the existence of an unknown substance, thought to be of nutritional importance and a constituent of the protein molecule. The present authors sought to show a relationship between substances found in proteins and vitamin D and their presence, not in all, but only in certain, purified proteins. In the experiments animal proteins employed included those of milk, ox blood, egg, muscle and lactalbumin, liver albumin and globulin, casein and gelatin. Vegetable proteins comprised edestin, oryzenin, hordein, wheat, corn, pea and yeast. All these were prepared by standard methods, vitamins being removed as far as possible, and hydrolyzed. The hydrolysates' effect on bacterial growth showed that, of animal proteins, only casein and commercial gelatin definitely stimulated growth of streptococci, while of vegetable ones only edestin and yeast protein supported the same.

A method was devised for determining the amount of the active substances with the aid of Sørensen's indicator method, which is based on change in pH due to the bacterias' fermentative action. The method



is a comparative and not a quantitative one. Yeast protein hydrolysate was found richest in active substances, casein, commercial gelatin and edestin following in the order named. Regarding yeast cells all hydrolysates except casein and yeast protein either failed to stimulate growth or inhibited the same. Regarding proteins whose hydrolysates gave no growth stimulation it is pointed out that the method of preparation and purification possible in their case appears to have freed them from vitamins (excepting edestin). Experiments with a neutral sodium caseinate solution also tend to show that the active substance in the protein is not necessarily a constituent of the protein molecule. The authors conclude that substances are obtainable from casein, commercial gelatin, yeast protein and edestin by hydrolysis that stimulate growth of hemolytic streptococci markedly and that this action is due, not to any constituent of the protein molecule, but to adsorbed vitamin retained in spite of purification, the amount present depending on method and degree of purification. The active substances are probably related to, if not identical with, water-soluble vitamins from brewers' yeast, particularly vitamin D.

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(1d—98)

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**A New Material for the Preparation of Bacterial Nutrient Media.**

*K. Thilo, Deutsch. med. Wchnschr., Leipsic, 48:868, June 30, 1922.*

The chemical factory of Chr. Brunnengräber, in Rostock, manufactures a substitute for peptone nutrient media, which are now extremely expensive. This new substance is prepared from yeast, which is considerably cheaper; a yeast extract (pepkam), a yeast peptone (pepkam), and a basic nutrient medium (pepkuro) are prepared. Extensive experiments have proved that the new nutriment media are fully as good as the old ones. Instead of 10 gm. peptone Witte and 10 gm. meat extract, 18 gm. pepkuro are employed.

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**A Method of Detecting Rennet Production by Bacteria.**

*H. J. Conn, J. Bacteriol., 7:447, July, 1922.*

It is possible by the following simple method, devised by Conn, to avoid the weaknesses of the usual method of detecting rennet production by bacteria. Inoculate the culture under investigation into the milk in the usual manner; then incubate for 24 hours or such time as it is necessary to produce vigorous action in the milk with at least 0.5 c.c. of whey on the surface. Fresh milk of which 10 c.c. is placed in a test-tube is obtained at the end of the incubation period and it is unsterilized. This is warmed to 37° C., a measured quantity of whey from the incubated culture added and placed in a 37° C. incubator. Examine every 5 minutes for the first ½ hour and, if not curdled then, at less frequent intervals for a few hours longer. If rennet is present in any abundance, the milk is ordinarily curdled inside of ½ hour. By varying the quantity of whey added to the milk from 0.1 c.c. up to 1 c.c. and by recording the time necessary for coagulation, it is possible to make comparisons between different cultures on a quantitative basis.

The advantages of this method are that the unheated milk curdles readily and forms a typical firm rennet curd; that the peptonizing enzymes act more slowly and do not in any way obscure the curdling action of the rennet; and that the period of observation is so short that neither the bacteria present in the milk nor those added in the cultures have time to act on the milk themselves and the amount of whey added is too small to precipitate the casein by the action of any acid it might contain, hence the reaction occurring is due to the action of the enzymes alone. By the use of this method it is possible to obtain typical rennet curds from certain organisms ordinarily producing both acid and rennet and from others ordinarily digesting the milk so rapidly that no true curd could be observed.

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(1d—100)

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**Studies on the Action of Electrolytes on Bacteria. II. The Influence of the Trivalent Positive Salts on the Rate of Migration of Bacteria in an Electric Field, and Their Effect on Growth and Virulence of Pathogenic Organisms.**

*C. Shearer, J. Hyg., London, 21:77, June, 1922.*

Shearer describes a number of experiments which prove that bacteria in spleen broth or neutral Ringer's solution carry a negative charge and move to the anode in an electric field. By adding low concentrations of a positive trivalent ion such as lanthanum or cerium to the solutions containing the bacteria, it was found that the negative charge was immediately lessened or neutralized, and if the concentrations of these ions was still further increased the negative charge was completely abolished, and the bacteria underwent flocculation or agglutination. Living bacteria seem much more sensitive to the action of these ions than nonliving colloidal particles. The addition of negative trivalent ions, such as sodium citrate, to bacterial cultures is without any effect on their movement in an electric field; the negative charge on the bacteria is not increased.

Girard and Audubert in a recent paper give the results of some remarkable experiments with bacteria, in which lanthanum has been employed in very dilute solutions to reduce the normal negative charge on the cell wall. The reduction of this charge they claim is accompanied by profound alteration in biologic properties of the bacteria, viz. an increase in growth and virulence. Shearer performed a number of experiments along this line which gave inconclusive evidence in support of Girard's and Audubert's work.

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(1d—101)

(1d—101)

**Action of Dilute Acids in Blood Cultures.**

*I. Walker Hall, J. Path. & Bacteriol., Edinburgh, 25:297, July, 1922.*

From a study of the effect of acids on bacteria present in blood during an infection, Hall found that blood cultures could be accelerated by the addition of 1/200 normal solutions of lactic or nitric acids to ade-

quately buffered nutrient broths. By the following method it is possible to plate and identify within 24 hours. Two tall, narrow-necked bottles are filled with 50 c.c. nutrient sugar-free broth, with a buffer index around 3.0. The small inlet minimizes contaminations, and together with the depth of fluid, provides a sufficiently anaërobic condition in the lower parts, if, after sterilization, the bottles are plugged with sterile rubber stoppers. They can thus be used at the bedside. Just before use, to one bottle 1/400 of n. lactic and n. nitric acid is added, or, if preferred, 1/200 n. HNO<sub>3</sub>, n. lactic or n. HCl may be substituted. If sterile pipettes are employed, yielding 20 drops per cubic centimeter, then 2 drops of n. lactic, and 3 drops of n. nitric acid, or 5 drops of other normal acid solution suffice. For routine purposes, nitric acid is the best. The other bottle is free from acid and acts as the antibody content indicator. Five c.c. of blood are added to each bottle and shaken thoroughly. Both are incubated at 37° C. for 7 hours. Each bottle is then well shaken and standard loopfuls transferred to nasgar and blood agar plates. Next morning the colonies are identified and counted. If the nonacid broth does not yield any growth, it is replated each succeeding 24 hours. The relation of the respective numbers of colonies or the delay in appearance indicates the amount of bactericidal or other inhibiting factors and is a rough guide of the immunity present.

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(1d—102)

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**Quantitative Determinations of Some of the Biochemical Changes Produced by a Saprophytic Anaërobe.**

*L. D. Bushnell, J. Bacteriol., 7:373, July, 1922.*

By using a specially designed cultural apparatus, the author has attempted to obtain a more accurate classification of anaërobic bacteria than can be obtained by a study of cultural characteristics on various media and the ability to ferment certain carbohydrates. Using organisms isolated from spoiled canned asparagus, he utilizes as quantitative indications of difference the amount and kind of acid and gas produced from various carbohydrates, and the amount of proteolytic action determined by formation of ammonia and amino-acids. It was first necessary to obtain a medium which would be as constant as possible in composition and on which the organisms would grow. Then it was necessary to obtain an apparatus by means of which the various changes could be noted and recorded over a series of days, since the fermentations change with the age of the culture to a marked extent. As Bushnell found difficulty in using the apparatus described by other investigators he devised an apparatus which was used: To a quart milk-bottle, the culture vessel, was added 300-500 c.c. of the culture medium, followed by autoclaving at 20 lb. pressure for 30 minutes. In 300 c.c. of tap water 100 gm. of asparagus was suspended. The potato medium was made by adding to 300 c.c. water, 100 gm. potato which had been carefully selected, washed, peeled and passed through a meat grinder; the potato pulp was washed in running water for several hours. For the carbohydrate fermentation tests a 2% peptone solution was used. As an inoculum a 4 day old potato-peptone water culture of the organism grown at 37° C. was used. Just before inoculation the air is driven

out. Care must be taken not to shake up the medium during inoculation and sealing. After inoculation the cotton stoppers were removed and the bottles plugged with a No. 8 rubber stopper, fitted with 2 glass tubes, one of which served as an attachment for the vacuum pump and the other as a monometer tube. A perfect seal was made by covering the stopper with gauze, then with cotton, and this was autoclaved at 20 lb. pressure for an hour. After inoculation the rubber stopper is pushed firmly into the neck of the bottle and covered with a thick layer of rubber cement. Thin blocks of wood were placed on the top of the stopper, and all wired in place with iron wire. After the bottle had been fitted, it was placed in a special incubator at 37° C. and immersed in a copper tank containing heavy mineral oil. The lower end of the manometer tube was placed in a dish of mercury. The bottle was then exhausted as much as possible with a Geryk pump. When the mercury ceased to rise the tube attached to the pump was sealed and thus practically a complete vacuum as determined by the temperature and barometric pressure at the time was obtained.

To obtain samples of gas, uncontaminated with air, the mercury pump was attached to the sealed tip mentioned above. A tight fitting rubber stopper was first placed over the tip and the rubber connection forced carefully over the tip until the metal tube came well down over the tip. This was wired firmly in place. A larger tube filled with mercury was fitted and the connections thereby completely covered. When the entire apparatus was completely exhausted, the connection at the sealed tip was broken. The mercury immediately falls in the pump and there is a corresponding rise of the mercury in the manometer tube. The gas is pumped out of the culture bottle and collected in a container over the mercury pump. Pumping is continued until the mercury column in the manometer tube becomes stationary. This is usually very close to the theoretical vacuum, and required about 15-20 min. After the gas had been forced into the collecting bottle the connection between this bottle and the gas analysis apparatus was opened and the mercury in the gas burette lowered. By this means a sample of gas was drawn in, measured and analyzed. After the completion of the gas analysis, air was allowed to enter the apparatus through a cotton plug. After removal from the incubator a sample was taken for cultural purposes; stains, shakes and plates being made. The cultures were incubated several days at 37° C.

From the shakes and plates anaërobes were secured. This method has proved very satisfactory for the cultivation of anaërobic bacteria and for measuring the amount and kind of gas produced. The objection to the use of such an apparatus is that it does not give the anaërobes an oxygen when it is available. The quantitative results obtained in this Even the "obligate" anaërobes probably utilize a certain amount of free oxygen when it is available. The quantitative results obtained in this particular case do not happen to yield results of significance in the subdivision of the group of organisms studied. They do give a clear picture of the biochemical behavior of these types which will make possible an accurate comparison of their physiology with that of other forms. The author gives a discussion of the method and results obtained, together with numerous tables and cuts of the special apparatus employed.

(1d—103)

(1d—103)

**The Production of Viable Bacteria in Young Cultures with Especial Reference to the Technic Employed in Counting.**

*G. S. Wilson, J. Bacteriol., 7:405, July, 1922.*

Wilson gives a technic for the comparison of total and viable bacterial counts, which materially reduces the usual sources of error. An adaptation of the Helbe counting chamber to dark-ground illumination was used. Instead of examining the organisms in stained condition with open illumination they are observed in their natural state against a dark illumination. For use with a paraboloid condenser, the only required alteration of the chamber is a selection of a slide of such a thickness that the distance between the lower surface of the chamber and the upper surface of the condenser shall lie between 0.9 and 1.1 mm. With a slide of other dimensions than these correct focussing of the light rays becomes impracticable. The depth of the chamber is 0.02 mm., while the surface is ruled into small squares. The best combination of lenses has been found to be a two-thirds objective and an 18 compensating ocular. Preliminary dilution of the emulsion is made, the diluent used being a 1% solution of phenol in 0.9% saline. Immediate examination of the slide shows the bacilli standing out as light, refractile rods having a yellowish color, and having a certain amount of brownian movement which ceases in 10-15 minutes. The only serious drawback in the use of this method is that it is unsuitable for dealing with broth emulsions containing fewer than 50 million organisms per centimeter, but the majority of counts one wishes to make are concerned with much thicker emulsion.

The final technic of the viable count is described: Presuming a broth culture of an organism is to be counted, a certain amount of fluid is withdrawn by means of a dropping pipet, and 10 drops are delivered at intervals of 1 second between each drop into a flask containing a known quantity of sterile tap water at 18° C. After shaking thoroughly a fresh pipet is used to transfer 10 drops of this emulsion into a second flask, also containing a known quantity of tap water at 18° C. The quantity of water in each flask will vary according to the age of the culture which is to be counted; in any case, the quantity is delivered by means of a calibrated volumetric pipet. When the second flask has been shaken, 4, 8 or 12 drops of this emulsion are delivered into 3 test-tubes, measuring 6 in. by  $\frac{5}{8}$  in., each containing about 2 c.c. of melted agar at 45° C. The contents are then mixed by gentle shaking, and the tubes are rolled by rotation between the fingers. The tubes are incubated in an inverted position for 3 days at 37° C. and at the end of that time are counted. In order to count the number of colonies which appear, a series of circles, 1 cm. apart, is lightly drawn around with an oil-marking pencil, and a longitudinal line drawn from one end intersecting each circle at right angles. The actual count is made by means of a small magnifying glass, the tube being held against a dark background illuminated by a partially concentric bulb. The experimental error involved in each count does not exceed 5%.

It is then applied to the study of the relation between the living bacteria in a culture and the total number of organisms alive and seen that even during the logarithmic phase the percentage of



viable organisms seldom rises above 90% of the total. To explain this, a hypothesis is advanced which supposes that in an in vitro culture of *Bacterium suipestifer* there is a normal death-rate amongst the bacteria, even during the logarithmic phase of growth. Assuming the presence of a normal death-rate, it has been possible to calculate the generation time on an altered basis, and this time has been found to be shorter than that usually given for cultures of similar organisms.

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(1d—104)

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**The Relation of Bacteria to Mucous Membranes.**

*Arthur L. Bloomfield, Bull. Johns Hopkins Hosp., 33:252, July, 1922.*

Bloomfield continues his studies of the dissemination of the bacteria in the upper air passages, with a series of experiments undertaken to determine the reason why certain bacteria are found constantly on the human tongue, while others colonize temporarily, and still others cannot be made to grow there. In the first experiments it was attempted to remove the harmless organisms of the tongue by scrubbing and irrigating its surface. Vigorous and long continued scrubbing failed to modify the cultures obtained, nor could freedom from organisms or even marked reduction in number be gained by attempts to draw the organisms out with hypertonic salt solutions, nor by dissolving off the mucus with sodium carbonate. It is evident that the germs are growing in an intimate way on the tongue, probably actually within the mucous membranes. In other experiments it was attempted unsuccessfully to colonize foreign bacteria (*Sarcina lutea*, etc.) and even to colonize organisms actually recovered from the same tongue. These could not be made to grow there in proportions different from those found when the original cultures were made. The conclusions are that no bacteria entering the mouth can persist free in the secretions for more than a few hours, and that more permanent presence implies a biologic adjustment to growth on the mucous membranes whereby the organisms become localized at the site of growth. Such adaptive power is relatively constant for large groups of bacteria in relation to the general population, but varies widely in the case of individual organism and individual host.

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(1d—105)

**The Hemolytic Organisms of Normal Infants' Feces.**

*E. W. Todd, J. Hyg., London, 21:37, June, 1922.*

This investigation was undertaken primarily to determine the frequency with which hemolytic strains of streptococci and *Bacillus coli* occur in normal infants' feces. The biochemical reactions of all the strains of streptococci which were isolated were also investigated and some observations were made on the occurrence of anaërobic organisms. The infants from whom feces were obtained were all under 1 year of age, and at the time when the stools were taken they were in good health, their motions being of normal consistency and appearance. There were 78 normal breast-fed infants and 13 who were artificially fed. The author examined 101 stools, which were dried by Dudgeon's method as detailed by Wordley. The heat resistance of the strepto-

cocci was examined by the method employed by Wordley. Tables are given which show the percentage of stools from each age period which contained streptococci, *B. coli*, staphylococci or anaërobic organisms.

Todd found streptococci present in the stools of all babies more than 3 weeks old, but only 3 hemolytic strains were isolated, which appears to be a lower proportion than occurs in adult stools. Colon bacilli were found in the stools of all babies more than 2 weeks old, and hemolytic strains occurred in 12% of the specimens examined, i.e. in the same proportion as in adult stools. *Staphylococcus albus* was much more commonly found than in adult stools and in greater abundance. There was no bacteriologic difference between the stools of the 78 breast-fed babies and those of the 13 artificially fed infants, except that the hemolytic strains of *B. coli* occurred relatively more frequently in the case of the artificially fed infants but owing to the small number of hemolytic strains isolated it would be unwise to lay too much stress on these figures, Todd concludes. There were no entamebas, cysts, or other parasites found.

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(1d—106)

***Clostridium Botulinum.***

*Fred W. Tanner and Gail M. Dack, J. Infect. Dis., 31:92, Aug., 1922.*

After the relation of *Clostridium botulinum* to food poisoning had been established, the attention of bacteriologists was directed toward a better understanding of the characteristics of the causal organism. The object of this work was to seek information concerning the reaction to heat, and the natural habitat of the organism. Tests were made on 5 cultures isolated from various sources. Since the organism forms spores which are resistant to moist heat, the efficiency of dry heat sterilization in destroying the spores was tried. The different strains of *C. botulinum* showed different resistance to dry heat; at 110° C. the time of survival averaged beyond 120 minutes; at 140° C. the variation was between 60 and 15 minutes; and 160° C. and 180° C. the times of survival were short, 5-15 minutes.

The modern methods of dry heat sterilization seem to be adequate for sterilizing apparatus which has been used for collecting *C. botulinum*. Young spores are more resistant to dry heat than old ones. Like other pathogenic anaërobes, *C. botulinum* is commonly present in nature; of 73 samples of soil, 11 contained it; 3 specimens of hog feces contained it, but it was not isolated from 3 specimens of cow feces. It was found in one sample of sewage. It is probably a common saprophyte and widespread in nature, and is perhaps more common in freshly manured soils. The occurrence of the organism in the stools of healthy individuals is now being studied.

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(1d—107)

(1d—107)

***Diphtheria and Pseudodiphtheria Bacilli.***

*M. Pergola, Policlinico (Pract. Sect.), Rome, 29:969, July 24, 1922.*

A question not yet answered is that of the differentiation of the diphtheria bacillus from the pseudodiphtheria bacillus. In this pre-

liminary note the author states that by the use of a culture-medium of his own composition, made from tellurium (of which he does not give the details), for cultures of isolation and concentration, he has been able to observe, in material coming from active patients, colonies that are typically diphtherial. In material coming from convalescent patients, or from those fully cured clinically, or from individuals who had had contact with diphtheria patients, he found colonies that were microscopically identical with those of diphtheria, but which were microscopically composed of elements which in their morphologic characteristics must be referred to pseudodiphtheria, owing to absence or scarcity of metachromatic granules. Even these bacilli, according to Pergola, must be considered as diphtheria bacilli that have undergone modification either because of their long stay in the organism, or because of diphtheria antitoxin, or of some other circumstance whose nature eludes us. They must be considered as of diphtheria stock, in a modified condition. Some pseudodiphtheria strains, however, in the cultures prepared by the author, became clearly differentiated both from the typical diphtheria bacilli and the modified organisms.

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(1d—108)

(1d—108)

**Cultural Methods for the Gonococcus.**

*John C. Torrey and George T. Buckell, J. Infect. Dis., 31:125, Aug., 1922.*

In order to make a serologic study of the gonococcus it was necessary to devise methods and mediums whereby the organism might be readily isolated and a large collection of strains maintained with a minimal risk of any of them being lost. Three mediums were used in this work. Ascitic-veal-urine-glycerol-agar was used as a plating medium, and was found effective in the isolation of the gonococcus, especially when combined with the dye, iodine-green. Two others were used, one ascitic, salt-free, 1.5% peptone, "vitamin" agar was used in isolating the organism, the other, which did not contain ascitic fluid, was used to maintain the stock strains. They lived on this medium without replanting for several weeks. It was found that for the optimal growth of the gonococcus the reaction of the medium should be set close to the point of absolute neutrality, between pH 6.8, and 7.4. The reaction range compatible with growth on a semisolid medium containing a growth accessory factor was found to extend from pH 5.8. to 8.2.

A slightly acid reaction was found to be more favorable to growth than a slightly alkaline reaction. One strain seeded on a semisolid "hormone" agar (Huntoon) with a primary reaction of pH 6.3 lived for 1 year. No better growth was obtained by the use of a medium containing a high concentration of amino-acids than when prepared with the specified amount of peptone. The presence of glucose does not enhance the growth of the gonococcus. The growth stimulating principle in a medium prepared according to Huntoon's method was found to be slightly impaired by exposure in the autoclave to 120° C. for 5 minutes and seriously injured but not entirely destroyed after 15 minutes at this exposure. Abundant moisture in the air of the incubator is a prime requisite for the optimal growth of the gonococcus,

especially on first isolation; but a reduced oxygen tension was not found to be advantageous. Fermentation tests constitute the most valuable single criterion for the differentiation of gonococci from other Gram negative diplococci. No one of 86 strains tested split maltose and all but one fermented glucose. None of those tested on levulose and galactose split these sugars. A sugar-free semisolid ascitic agar medium with brothymol-blue as indicator proved satisfactory as a base for fermentation tests.

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(1d—109)

(1d—109)

**Contributions to the Bacteriology of Leprosy. I. The Diphtheroid in Leprosy.**

*Ernest Linwood Walker, Am. J. Trop. Med., 2:293, July, 1922.*

The first purpose of this investigation was to substantiate the more or less constant cultivability of a pleomorphic, partly acid-fast diphtheroid from leprous lesions. The material was obtained from lepers confined in the San Francisco Isolation Hospital, and was chiefly from nasal ulcerations and occasionally from open leprous lesions in the skin. In a few cases aseptic incision of nonulcerating leprous nodules was performed. In 312 cultivations from the nose and open skin lesions of 16 lepers, 4 types of diphtheroids have been encountered, which can be distinguished from one another by colony characters, carbohydrate fermentations, morphology and staining peculiarities.

Efforts were next directed to discover a possible saprophytic source of this diphtheroid as bearing on its parasitism and etiologic relation to leprosy. Whether or not the conclusion is accepted that the diphtheroid cultivable from smegma praeputii is *Bacillus smegmatis* is immaterial, since in either event the essential fact remains that this diphtheroid from smegma possesses cultural, morphologic, biochemical and tinctorial characteristics which are apparently identical with those of the diphtheroid cultivable from the lesions and organs of lepers considered by some authors as the cultural form of *Bacillus leprae*.

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(1d—110)

(1d—110)

**The Action of Staphylococcic Bacteriophages.**

*Tai Watanaba, Wien. klin. Wchnschr., 35:603, July 6, 1922.*

In the examination of the pharyngeal secretion of a diphtheria suspect, the agar plates revealed streaks of a predominantly yellow mixed culture containing staphylococci, the first of which presented spaces. When the staphylococci were cultivated on slants or agar plates, the resulting bacterial colonies always presented these spaces, frequently in great numbers; these could be further cultivated by transplantation; when they were transferred to meat broth, there was not only absence of increase, but even a disappearance of these formations, which were unquestionable bacteriophages.

If a suspension was prepared from an agar colony containing spaces, and placed upon an agar plate over which a normal staphylococcal suspension had been uniformly distributed and dried, the resulting staphylococcus colonies, when maintained at 37° C., presented either large spots, free from typical growth, or a number of spaces, according

to the dilution employed. However, neither the spots nor the individual spaces presented surfaces actually free from growth, as is the case, under similar conditions, with Shiga bacteriophages on a Shiga plate. There was, on the other hand, a thick growth of comparatively delicate and small colonies, which were white rather than yellow, with the occasional admixture of ordinary yellow staphylococcus colonies.

Microscopically these delicate colonies presented cocci which, on the whole, entirely resembled those of the yellow strain, or appeared to be somewhat smaller. They could be cultivated in the same form on agar, and also grew in meat broth. In the broth, however, in the first generation, especially when the culture was inoculated with large quantities of the white cocci, bacteriophages appeared, i.e. when such a broth culture was transferred to a plate with yellow staphylococci, free spaces and holes appeared in continuity with the coccal colonies. On the other hand, the white cocci were completely insensible even to this bacteriophagic action on the agar plate. The insensitivity, as well as the aberrant form of growth, persisted unchanged through 20 cultivations on agar; however, reversion to the yellow racial form appeared in some of the colonies, frequently as early as the first or third series. These retrograde forms were capable of cultivation to a pure type which was again sensitive to the bacteriophagic action.

Without doubt the accidental discovery of staphylococcal bacteriophages in material to be examined bears a relation to the analogous findings of Twort and Gratia, who isolated staphylococci from measles vaccine; no complete analogy can be proven. There are important differences between these bacteriophages and the staphylophages opposing other bacteria, e.g. Shiga bacilli. These differences support the assumption that a low form of development of bacteriophagic activity is involved.

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(1d—111)

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**The Loss of Hemolytic Capacity by a Fraction of a Culture of a Hemolytic Streptococcus without Change in Agglutination Characteristics.**

*Eugenia Valentine and Charles Krumwiede, J. Exper. Med., 36:157, Aug. 1, 1922.*

The authors report comparative observations on a strain of hemolytic streptococcus which has developed a nonhemolytic fraction. This strain, originally isolated from the lung at autopsy (bronchopneumonia following measles), has been maintained on blood-streaked agar. For more than a year it was plated on poured and streak blood agar plates at frequent but irregular intervals, without change. Subsequently, it was found that 10% of the colonies showed no evidence of hemolysis but resembled closely a pneumococcus colony. The hemolytic fraction has all the characteristics of the beta types with a 4-5 mm. transparent zone of hemolysis. The green fraction is an alpha type with no visible clearing except for the late development of a narrow green translucent zone. The surface colonies of the latter are moist, green-zoned, and resemble closely a typical pneumococcus colony. Aside from these differences, the 2 fractions are alike morphologically and culturally.

Agglutination tests were set up with the serum of a sheep immunized against the original strain. Both fractions were agglutinated



equally well, and to the titer of the serum strain. Likewise absorption of this serum by either fraction removed completely the agglutinins for both fractions and for the serum strain. Additional serums for agglutination and agglutinin absorption tests were obtained from rabbits immunized with a representative of each of the fractions. The results demonstrate the ability of either fraction to absorb agglutinins from the antiserum of the other fraction and show that the loss of hemolytic power was not accompanied by any change in the agglutinogenic complex of the cocci.

The virulence of the 2 strains was tested by mouse inoculation with 18 hour broth cultures; 0.5 c.c. of the hemolytic organisms killed uniformly, 0.25 c.c. irregularly. The green type was less virulent, 1-1.5 c.c. causing death, but only irregularly. Increased virulence, through mouse passages, of the green variant was not associated with development of hemolytic colonies. An attempt to restore hemolytic capacity to the green variant by successive transfers in blood broth was unsuccessful. Variations in the physiologic functions of bacteria occur with frequency. However, general experience indicates a high degree of stability of bacterial types as regards the antigenic qualities of their body substance. This study is offered as additional evidence in favor of the hypothesis that functional changes among bacteria are, at most, only infrequently associated with changes in the antigenic matrix of bacteria.

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(1d—112)

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**Investigations on the Nutrition, the Formation of Strains and Immunity of Streptococci.**

*Max H. Kuczynski, Klin. Wchnschr., Berlin, 1: 1413, July 8, 1922.*

The origin of *Streptococcus viridans* from hemolytic strains is due to an inhibition of cellular capabilities. The normal body of the mouse or a homologous immunization may produce this inhibition. In the surviving blood, which develops a marked bactericidal power against streptococci, the viridans forms are seen after 24 hours either alone or with the hemolytic forms. The same result is achieved in actively immunized guinea-pigs and rabbits: after the injections of hemolytic streptococci a rich green growth is obtained in a short time, but this is no longer demonstrable later because of the great bactericidal properties of the rabbit. From this the author concludes that the immunizing processes are of a natural sort or induced by the proper treatment, which in the course of the infection develop the viridans phenomenon. The flightiness and slight power of resistance of these germs explains the variation in their pathogenic effects and also their local, disease-producing effects in contrast to the hemolytic forms. The inhibition leading to the viridans formation may arise when these particular ferments are poisoned or especially when they find no field for activity. For the culturing of the almost purely green pharyngeal flora, the author uses saponified myelins with the addition of the smallest amounts of peptids, maltose, serum, etc. Some of the hemolytic strains readily showed transition into the green forms of growth, others only after the slight addition of substances which produced that partial condition of starvation which seems necessary for the development and maintenance of viridans phenomena.

The proper conditions for growth for the hemolytic streptococci exist in the inflammatory exudate of the pharynx; after the subsidence of the inflammation, the nutrient medium is withdrawn from the rest of the germs through the effect of the cells and serum and they either undergo transformation or give way to the permanent green flora. The hemolytic forms as a rule require larger amounts of protein or the peptid stages of its decomposition; the viridans forms content themselves with slight amounts of decomposition in the lower stages. The viridans forms can live in the infected body on the traces of the circulating decomposition products of the food.

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(1d—113)

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**The Effect of Hydrogen-Ion Concentration on the Production of Carbon Dioxid by the Tubercle Bacillus.**

*Matilda Moldenhauer Brooks, Am. Rev. Tuberc., 6:369, July, 1922.*

This investigation, as indicated in the title, was suggested by the consideration that the different methods of using chaulmoogra compounds necessitate different degrees of acidity or alkalinity, and that the effects of the latter on the tubercle bacillus must therefore be studied first. The production of  $\text{CO}_2$  is used as a measure of the metabolic activity of the bacteria. The pH was changed by adding NaOH and  $\text{H}_2\text{SO}_4$  in various concentrations (thus keeping the volume unaltered). The pH indicators were thymol-blue, brom phenol-blue, methyl-orange, methyl-red, brom cresol-purple, phenolsulphonephthalein and phenolphthalein, which were found to be not injurious to the bacteria. The normal rate of production of  $\text{CO}_2$  (taken as 100%) represents the maximum production; it was measured by noting the time required (according to the amount of bacterial suspension used) to change the pH value of the indicator from 7.8 to 7.6. The results obtained with *Bacillus tuberculosis* were compared with those obtained with the nonacid-fast *B. subtilis* and the nonpathogenic acid-fast *B. butyricus*.

Under the influence of acid, the rate of production fell rapidly and then became constant; under the influence of alkali, there was an immediate cessation and then a gradual recovery, accompanied by an increase in pH. The slight metabolic activity of *B. tuberculosis* (as compared with the other 2) necessitated the use of large quantities of bacterial suspension, and because of the prodigious speed with which these bacilli neutralized the alkali, large amounts of the latter had to be added. It therefore became necessary to determine the share of the buffer action in the decrease of  $\text{CO}_2$  by control experiments. It was also noted that, after the addition of alkali to the microorganisms, the pH value gradually returned toward normal, accompanied by an increase in the rate of production of  $\text{CO}_2$ . The normal or maximum rate was found at pH 6 for *B. subtilis* and at pH 7.0 for *B. butyricus*, whereas, in the case of *B. tuberculosis*, it was found to remain unchanged between pH 4.4 and pH 7.4. Increase beyond pH 4.4 causes a decrease in the rate, which becomes constant in each case for a considerable time. Decrease beyond pH 7.4 causes a decrease in the rate, followed by a return toward the normal. *B. subtilis* is most

sensitive to the acid effects, as is shown by the steep decline in the curve of CO<sub>2</sub> production. The sensitivity of *B. butyricus* (which is less acid-fast than *B. tuberculosis*) is intermediate between the other 2. In the region of alkalinity, there is little difference in the behavior of the 3 microorganisms.

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(1d—114)

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**Cultivation of the Tubercle Bacillus by Petroff's Method in Dispensary Practice.**

*G. B. Roatta, Tubercolosi, Rome, 14:109, May, 1922.*

In 1915 Petroff described a new method for the cultivation of the tubercle bacillus from tuberculous sputum. This method was investigated, among others, by Calmette, who emphasizes the value of the procedure as one which enables the examiner to ascertain the presence of tubercle bacilli in suspected sputa much more rapidly and, what is more important, much more economically than by the usual methods of animal inoculation. In other words Petroff's method offers bacteriologists and clinicians a rapid and reliable means for the isolation of the tubercle bacillus from pathologic products containing other microorganisms, one that does away with all the various methods of concentration in cases in which direct examination gives negative findings. The great field of utility of this new method in dispensary practice, where it is frequently a matter of importance to establish quickly and certainly whether tuberculosis is present or not, a result not readily accomplished with the technic now employed, induced the author to use this new method as a control in looking for the tubercle bacillus in sputa obtained from patients of a tuberculosis dispensary.

The last 10 cultures of sputa obtained from dispensary patients, all of which had been positive (with varying degrees of intensity) on direct examination, gave these results: 3 specimens were frankly positive, the growth being particularly noticeable at the base of the culture medium; 2 specimens showed 3 or 4 colonies of ordinary cocci, with a separate discreet area—at one side—of small colonies of tubercle bacilli; 3 remained sterile; and in the remaining 2 plates a spore-bearing bacterium of the subtilis type grew so luxuriantly that on the second day its colonies had covered the entire surface of the medium. These findings lead the author to the conclusion that Petroff's method cannot be of very great practical value for diagnostic purposes in dispensary practice, although it is to be preferred to all other methods on account of greater simplicity of execution, facility of technic and economy of materials whenever it is desired to obtain a culture of tubercle bacilli directly from the sputum.

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**A New Method of Staining Tubercle Bacillus.**

*Antonio Luisi, Ann. d'igiene, Rome, 32:367, May, 1922.*

The technic of this method of staining is as follows: (1) The microscopic preparation is treated, warm, for 15 minutes with a saturated watery solution of crystal violet, to which is added at the moment of its use 3 or 4 drops of carbolic acid (5%). (2) Decoloration with

nitric acid, 40%, for only a moment. (3) Contrast staining for half a minute in a saturated watery solution of Orange G. With this method, quite rapid and simple, there are obtained, above all, preparations in which the bacilli, of an intense violet color, stand out prominently on an orange-yellow background. These present, in addition, their characteristic shining granular appearance, in a number very much greater than by any other method. On the yellow-orange background the other organisms are not visible. The solutions remain good for a long time, and the preparations are lasting.

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(1d—116)

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**The Decoloration of the Tubercle Bacillus with Sodium Sulphite.**

*J. von Bergen, Rev. méd. de la Suisse Rom., Lausanne, 42:429, July, 1922.*

The author has thoroughly tested the sodium sulphite method of decolorizing. The fuchsin solution is usually prepared freshly every day. Before decolorizing, the specimen is again heated, in order to redissolve suspended particles. When the slide has been cooled, it is plunged, without previous washing, into baths of 1% and 10% sodium sulphite solution, containing no alcohol. The same treatment may be followed by immersion in 60% alcohol, if desired. The sulphite method has been tried with tubercle bacilli of various origins and with smegma and other acid-fast bacilli. The results were compared with those obtained with 5% nitric acid, followed by alcohol. The sulphite was tested for various periods up to 4 days. For good decolorizing, the sulphite solution must act for at least 30 minutes. A satisfactory result may be obtained in a few minutes by following the sulphite solution with 60% alcohol. Since the sulphite readily decomposes, its solutions must be perfectly fresh. Fresh 1% and 10% solutions of sulphite, followed by 60% alcohol, decolorize as well as dilute sulphuric, hydrochloric or nitric acid, and act more delicately upon the material examined. In general, the Ziehl-Neelsen staining method is superior to all others.

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**Studies in Bacterial Variability. The Experimental Production of a Mucoid Form of B. Paratyphosus B.**

*E. W. Ainley Walker, J. Hyg., London, 21:87, June, 1922.*

The experimental derivation of a mucoid form of *Bacillus paratyphosus* B was produced by growing an ordinary paratyphoid B bacillus in an environment containing about 25% of specific immune serum. This form, though at one stage nonmotile, agreed closely with the capsulated mucoid forms of paratyphoid B, isolated by W. Fletcher from 2 chronic carrier cases. That the cultures originally used were actually cultures of *B. paratyphosus* B and not accidental contamination was proved by the fact that, after subcultivating the bacillus from the mucoid culture, which had rested in agar stab for about 3 months,

through a succession of bouillon cultures it yielded on plating out on agar, a proportion of typical colonies of *B. paratyphosus* B, whose formolized suspensions agglutinated normally with standard agglutinating serum. Subsequently, by continuing the serial subculture in bouillon, the whole culture was brought back (in 6 weeks) to the eu-agglutinable phase. A plating made at this stage showed a mixture of "rough" and "smooth" colonies of the ordinary type, along with 2 colonies which were like smooth colonies, except that they exhibited umbilication.

A formolized bouillon culture prepared from an umbilicated colony was highly dysagglutinable, and gave no more than traces of agglutination in 1:50 dilution of standard paratyphoid B serum. Its colonies were also entirely unlike colonies of paratyphoid B, being large, slimy and unusually dome shaped, though at other stages of their metamorphosis they presented either an umbilication, or a nipple-like elevation in the center. The mucoid bacillus possessed the distinctive sugar reactions of paratyphoid B.

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**The Culturing of *Rickettsia Prowazeki*, the Excitant of Typhus, on Solid Media.**

*Max H. Kuczynski, Klin. Wchnschr., Berlin, 1:1412, July 8, 1922.*

Up to the present time, the culturing of the typhus virus has been possible only in a piece of infected tissue incubated in plasma culture; the author endeavored to obtain a culture independently of this piece of tissue. He used for the purpose slant agar cultures with the addition of serum from guinea-pigs, rabbits, sheep, horse, or swine. The implanted material must be rich in virus; small pieces of brain or spleen of the infected animal are immersed in normal salt solution or in a nutritive base and distributed to slanted test-tubes in amounts of 1 c.c. The tube is subsequently paraffined to maintain it in an atmosphere as moist as possible. It is almost never possible to obtain a growth in the first tube, but the contents of the same must be transplanted to other tubes at least once or even several times. Eventually, delicate, dewdrop-like cultures are seen on further inoculation, appearing as if the agar had been roughened—an almost veil-like growth, which disappears at the edge in single colonies; later it has a slimy appearance and a yellow or light gray discoloration. The cultures must be reinoculated at least every 43 hours; otherwise they degenerate, are no longer transferable and lose their pathogenicity for animals. Microscopically, the organism resembles the picture obtained from the louse but there are also pyriform, rod-shaped, thread and tube-shaped forms. With the Giemsa stain, blue, slender, tapering rods with 1 or 2 azure-red granules are predominant. The Gram stain is negative, that with anilin colors is weak and only the degeneration forms of older cultures readily take up fuchsin. In these older cultures, ring forms are also found and somatoid forms. If concentration is performed once, further culturing can be done with a simple nutrient base without the addition of serum. The odor is insipid and very characteristic. Positive results from inoculation were successful in the guinea-pig up to the sixth passage but the virulence is lost with the age of the culture.



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**Experimental Erysipelas. Studies in Streptococcus Infection and Immunity. IV.**

*F. P. Gay and Bernice Rhodes, J. Infec. Dis., 31:101, Aug., 1922.*

A strain of *Streptococcus pyogenes* originally obtained from a case of human empyema and raised in virulence for rabbits, by repeated passage through the pleural cavities of these animals, was used. This culture acquired new and relatively constant properties. It gained a marked pathogenicity for rabbits, whereas the original culture had little. Constant empyema was produced. Fatal septicemia usually resulted from large intravenous doses. A recoverable erysipelas was produced by intradermal injections in the back. Recovery from erysipelas from a period of about 3 weeks after inoculation produced complete protection against subsequent intradermal inoculations. This protection usually lasted at least 3 months. Repeated injections and vaccines from the passage strain killed by heat and alcohol, did not protect. Oil vaccines in the same amount frequently gave protection. Several injections of the original living stock culture, which produced no lesions, gave protection against the passage strain. Complete protection against intradermal inoculation by previous intradermal infection or immunization frequently did not protect against intravenous infection. The reverse set of conditions also prevailed. These facts point strongly to the existence of a true local tissue immunity following streptococcus infection or immunization.

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**The Pathogenicity of *B. Melitensis* and *B. Abortus* for Guinea-Pigs. Studies on the Genus *Brucella* Nov. Gen. IV.**

*K. F. Meyer, E. B. Shaw and E. C. Fleischner, J. Infec. Dis., 31:159, Aug., 1922.*

In order to verify preliminary observations 22 strains of *Bacillus melitensis* were tested on guinea-pigs. The injections were made either into the abdominal cavity or into the parenchyma of the testicle. The course of the infection was followed by regular weight determinations and skin tests. When the animals were ready for bacteriologic examinations they were chloroformed, necropsied and the lesions noted. Portions of the tissues were preserved for sections and cultures made from the spleen, liver, kidneys, lymph-nodes, bone-marrow, urine, bile, abscesses and bone lesions. The mediums employed were sheep-blood peptic digest agar plates, and peptic digest agar slants. Existence of infection in the guinea-pigs was considered proved by (1) positive skin reactions; (2) distinct anatomic changes in the liver and spleen; (3) microscopic changes in the form of focal lesions consisting of nests of actively growing epithelioid cells and connective tissue hyperplasia; and (4) positive serum reactions, particularly agglutination reactions in dilution above 1:100; the nature of the etiologic agent, whether *B. abortus* or *B. melitensis* was decided by (5) isolation of the bacteria from the tissues; (6) identification of the organisms by agglutination tests with serums specific for the various groups of the genus *Brucella*; (7) by absorbing the serum procured from the infected guinea-pigs with various antigens; and (8) by passage experiments.

It was found that certain strains of *B. melitensis* are capable of producing acute, subacute or chronic inoculation disease in guinea-pigs. The gross anatomic and the histologic changes resemble those commonly noted in guinea-pigs infected with *B. abortus*. It is sometimes impossible to distinguish the two infections without careful serologic cross absorption tests; 4 cultures infected guinea-pigs regularly, while 18 other strains proved either nonpathogenic or produced in exceptional instances lesions in the spleen and lymph-nodes. Aside from the inherent pathogenic properties of certain strains it is not unlikely that the individual susceptibility of the guinea-pigs and the mode of infection are in a large degree responsible for the course and character of the infection. Intratesticular injections were used most frequently. Of the 44 guinea-pigs sacrificed 44-155 days after injection, 34 presented advanced tuberculosis-like lesions in the spleen and lymph-nodes. The lesions produced in guinea-pigs with *B. melitensis* are usually less extensive and severe than those produced by *B. abortus*. These experiments show that *B. abortus* may produce in guinea-pigs an interesting inoculation disease. The degree of tissue injury in the spleen and lymph-nodes may vary considerably.

Sexotropism, which follows any form of inoculation whether caused by infected material or cultures, is remarkably constant. Infections involving all the tissues of the body with the exception of the muscles were characteristic for a strain of *B. abortus* isolated from an aborted swine fetus. Enlargement of the spleen was noted in guinea-pigs injected with infected milk or tissues. Old laboratory cultures usually produce lesions so slight that they cannot be seen with the unaided eye. This group of cases resembles anatomically the infections caused by intratesticular or intraperitoneal injections of certain *B. melitensis* cultures. Recently isolated strains and particularly cultures or milk specimens obtained from goats with Malta fever should be tested for pathogenicity on guinea-pigs.

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**Studies on Mediterranean or Malta Fever.**

*E. Burnet, Arch. d. Inst. Pasteur de l'Afrique du Nord, Tunis, 2:165, April-June, 1922.*

Guinea-pigs may easily be infected with *Micrococcus melitensis* by mouth, or by inoculation subcutaneously or upon the scarified skin. No fever like that occurring in man appears. It is not sure that the rise of temperature, rarely occurring, is due to the infection. Agglutination is most marked in the serum of animals most severely affected with abscess and mammary and glandular lesions. It declines, after a considerable time, in animals inoculated through the heart. The micrococcus does not constantly appear in the blood and urine, but accompanies infective exacerbations and elimination. It is constantly present in the lymphatics, spleen and bone-marrow, rare in the liver, kidney and suprarenals and has not been found in the bile. The glands, spleen and bone-marrow serve to harbor the bacterium. The latter produces persistent abscesses in various regions, or may cause nonpurulent granulations like pseudotubercles. It has been found in the spinal cord of paraplegic guinea-pigs. During lactation, the micrococcus does not especially affect the mammary gland and but rarely enters the milk.

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The young born of profoundly infected mothers are not infected at birth, and only rarely through the maternal milk. They may be sometimes infected through infected bedding. Agglutination present at birth rapidly declines, ceasing usually by the fortieth day. Osteitis and arthritis are frequently produced. Arthritis of the knee resembles white swelling. The primary lesion is probably osteomyelitis, which extends. Infection in guinea-pigs, unlike that in man, is similar to that occurring in goats. The undulating character present in the fever produced in man accompanies other symptoms occurring in the guinea-pig. In the latter, the characteristics are chronicity, constancy and persistence of the regions harboring the micrococci, and steady general sickness. Rabbits were infected by subcutaneous inoculation and simple instillation into the conjunctival cul-de-sac. Fever was not produced. Agglutination by the serum was high (2000). Rabbits are less susceptible than guinea-pigs, but suppuration is more frequent.

In view of the tendency of Malta fever to produce a constitutional state, analogous with that present in tuberculosis, it occurred to the author that an intradermal reaction might prove valuable. If infected man or guinea-pig be inoculated with *Micrococcus melitensis*, general and local reactions, similar to those of tuberculosis, occur. The local reaction, consisting of edema, slight pain and redness, is produced by intradermal inoculation of 0.1 c.c. bouillon culture filtered with a bougie. This reaction is simple, sure and specific, in man and guinea-pig. The subcutaneous inoculation of 0.25 c.c. filtrate produces specific edema accompanied by pain. Application of the filtrate to the unbroken skin gives no result. The intradermal inoculation is negative in rabbits. The bouillon becomes active by the eighth day of culture growth. Any laboratory bouillon is satisfactory. The filtrate used for inoculation must be proved sterile by test, consisting of inoculation of the filtrate in gelose. In practice, the filtrate employed for the intradermal reaction should be obtained from cultures grown for about 20 days.

Malta and Tunis are the most important centers of Malta fever. Positive serodiagnoses indicate that human infection at Tunis, begun in 1915, is increasing. Infected goats of the Tunis herds have increased from 4.02%, in 1909, to 9.1% in 1921-22. Formerly, infection was more common in Malta than in Arab goats. In 1921-22, in herds of the same locality, the Arab-goat infection was 9.7%, the Malta-goat infection 3.3%. In any infected goat, the agglutinating power and results of cultures made from blood and milk vary greatly. The sickness occurring in goats is incompletely known, since the clinical, anatomic and bacteriologic observations are thus far inadequate. Goats infected artificially do not seem to recover.

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**Studies upon Experimental Measles. II. The Enanthematous, Exanthematous, Pyrexial, and Leukocytic Syndrome Produced in the Rabbit by Intravenous Inoculation of Blood from Cases of Human Measles.**

*Charles W. Duval and Rigney D'Aunoy, J. Exper. Med., 36:231, Aug. 1, 1922.*

The purpose of these experiments was to determine whether the virus of measles could be propagated in the rabbit by direct transfer  
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of infected blood from man, and also to ascertain whether in this animal the experimental infection would induce the characteristic syndrome of the human disease. Defibrinated human blood obtained from measles cases at the stage of temperature height was used for inoculation, within 1 hour after withdrawal from the body. Intracirculatory injection in rabbits was made into the marginal ear vein, or, occasionally, by cardiopuncture. The authors regard as pyrexia in the rabbit only the reading about 103° F. Leukocyte counts below 9000 are considered as evidence of leukopenia.

The results show that an active transmissible virus exists in the blood of measles patients during the eruptive stage of the disease. This virus produces, in 90% of rabbits inoculated, a specific reaction analogous in all essential features to that of the human infection. Following a definite incubation period of 2-5 days the animals infected show pyrexial, leukocytic, and cutaneous alterations. The earliest symptom is rise in temperature, occurring about 4 days after inoculation, associated with relative or absolute leukopenia. The most striking objective signs are the coryza, conjunctival injection, enanthemata, and exanthemata. The mucous membrane lesions, appearing coincidentally with pyrexia or shortly thereafter, are similar in their physical picture to the Koplik spots in man. The typical exanthematous rash appears on the third to seventh day after inoculation. Only 40% of the injected animals develop the skin eruption. Repeated passage through the rabbit seems to increase the virulence of the infectious agent. A number of animals infected with such passage virus succumb in the fourth and subsequent generations, undoubtedly as the result of the specific excitant, as none of the animals developed any discoverable intercurrent infection. In the animals so dying grave nephritic changes were evident. It is noteworthy that pneumonia was not found in any of these animals.

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**Studies upon Experimental Measles. III. The Symptom-Complex in the Guinea-Pig and Rabbit Following the Intratracheal and Intravenous Injections of Filtered Nasopharyngeal Secretions from Cases of Human Measles.**

*Charles W. Duval and Rigney D'Aunoy, J. Exper. Med., 36:239, Aug. 1, 1922.*

In this study the authors desire to record the reaction produced in guinea-pigs and rabbits as a result of introduction into their circulatory and respiratory systems of filtered nasopharyngeal washings from cases of human measles. Nasopharyngeal secretions were secured from cases of the human disease at the height of the cutaneous reaction, by means of West tubes. The applicators were washed in small portions of 0.85% sterile saline in order to obtain as concentrated washings as possible. Filtration of washings was made through Berkefeld N filters, the filtrate in all instances showing no ordinary bacteria. From the time of securing washings to the time of animal inoculations not more than 1 hour elapsed. Under ether anesthesia, as much as 10 c.c. of washings were injected intratracheally in a full grown rabbit without subsequent discomfort to the animal. In rabbits the material was

injected into the marginal ear vein and in guinea-pigs it was administered by cardiopuncture.

As a result of the experiments it seems conclusively established that intratracheal and intracirculatory introductions in guinea-pigs and rabbits of filtered nasopharyngeal secretions from cases of human measles occasion a definite and constant reaction, characterized by a complex of objective and subjective signs which closely resemble the manifestations of measles in man. Enanthem, exanthem, and pyrexial disturbances characterize the specific reaction in rabbits; in the guinea-pig the reaction manifests itself by pyrexia, marked leukopenia, and grave nephritis in the fatal cases.

The regularity with which it has been possible to produce this symptom-complex in animals with the filtered nasopharyngeal washings, and its similarity to human measles and the experimental disease induced in animals following the intracirculatory injection of infectious human blood led to the conclusion that there is present in nasopharyngeal washings of measles cases, as a causal agent of the disease, a filter-passing virus. The authors believe that experimental measles is primarily an infection of the blood, and that the mucous membrane lesions are secondary. If the localization of the specific incitant took place in the mucous membranes by selective action, it would seem plausible to expect earlier manifestations following the direct infection of mucosal surfaces than following infection by the intracirculatory route.

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#### **Etiology of Scarlet Fever. IV. Variation or Types of the Alkali-Producing Organism in Scarlet Fever.**

*R. W. Pryer, J. Lab. Clin. Med., 7:592, July, 1922.*

In three previous papers the author reported the isolation of a peculiar organism from infectious discharges of scarlet fever cases. In the course of the investigations it was found that young cultures of this spore producing coccus-like organism are spore free and that under certain conditions when the organism is carried on artificial culture media considerable changes in morphologic and serologic characteristics occur. In this paper an attempt is made to determine something of these mutation or cyclic changes and how they may be brought about.

When freshly isolated from the human being the organism differs in size, morphology, and in other ways from the end-forms described in previous reports. That it does not produce spores when living as a parasite in the body of the patient is very probable. This can be attributed to the fact that the spore bearing coccus form, when growing in symbiosis with other organisms present in the discharges from the throat, nose, ear, glands, etc., fails to yield spores.

A change in morphology was noted in cultures isolated from guinea-pigs succumbing to inoculation of these cultures. If death ensues in a day, cultures from heart's blood or peritoneal cavity usually show the large spore bearing coccus form. The organism recovered from animals dying on the second to fourth day following injection is usually a peculiar small coccobacillus. These strains, as a rule, produce alkali in the different sugar media. They fail to agglutinate with specific serum for the spore bearing group. Postmortem cultures



on animals dying several days after inoculation frequently yield a hemolytic type of organism, apparently identical with the beta type hemolytic streptococcus. These hemolytic organisms when grown in alkaline sugar media pH 7.8 at 37° C. gradually increase in size, and forms very similar to the spore bearing type may be seen, although no spores have been demonstrated and no alkali is produced in the cultures.

All cultures are planted on various sugar media, and the reaction observed for a long period of time. In one instance a series of cultures which had been in the incubator for several weeks were examined. It was found that one culture, No. 16, had changed from a small alkali-producing coccobacillus to the spore forming coccus-like organism.

Culture No. 16 usually presented what was apparently a mixture of cocci and bacilli, the culture being plated as high as 10 times in succession without separating these forms. The purity of the culture is attested to by the fact that after several successive animal passages the same forms were recovered. These purified cultures have subsequently changed to the large spore bearing coccus type.

An observation of significance with regard to this culture is that when transplanted daily for some days on Loeffler's medium, forms similar to Klebs-Loeffler bacillus were found usually predominating in the culture. These organisms, while resembling the Klebs-Loeffler bacilli in other respects, were frankly Gram negative. Nevertheless, an attempt was made to discover what effect diphtheria antitoxin had on animals inoculated with these strains.

Guinea-pigs of approximately 250 gm. weight were each inoculated with the same dose of a saline suspension of these diphtheria-like organisms grown on agar slants. The animals were then divided into 3 groups. The first, or control group, receiving no antitoxin, invariably died. The second group were given diphtheria antitoxin at the same time as the inoculation; part succumbed and part survived. The third group received antitoxin in amounts of 200-1000 units 24 hours previous to the injection of organisms. All the animals of this group survived. This experiment has been repeated a number of times with identical results.

Culture No. 16, when grown under conditions favorable to development of diphtheria toxin, produced a substance poisonous for guinea-pigs, particularly for young animals 100-150 gm. in weight. Berkefeld filtrates of such cultures were toxic for guinea-pigs in doses as small as 0.1 c.c.

A considerable series of cultures of this type, serologically identical with culture No. 16, have been isolated from cases of scarlet fever. Despite that fact that Koch's postulates have not as yet been fulfilled, the author believes the experimental evidence obtained with all these cultures warrants the tentative conclusion that this variable organism is the cause of scarlet fever.

(1d—125)

(1d—125)

#### **Experimental Septicemia.**

*E. Delcourt-Bernard, Arch. méd. belges, Brussels, 75:520, June, 1922.*

In a series of experiments on dogs in which the animals were given one or more injections of peptone, followed by injections of nonvirulent

staphylococci and colon bacilli, it was found that the elimination of the microorganisms was delayed and disturbed by the anaphylactic shock caused by the peptone injections, and that the abnormalities observed were proportional to the intensity of the shock. The peptone injections prevented the adhesion of the blood-platelets in groups, but the microorganisms were eliminated independently of the changes in the platelets. The degree of leukopenia and the changes in the elimination of the microorganisms also were not parallel. The elimination of these organisms, therefore, the author concludes, does not depend upon any of the formed elements of the blood, but upon 3 factors: (1) the organic factor (humoral reactions), (2) the microbial factor (virulence), and the nature of the substance interfering with their elimination.

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(1d—126)

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**Experimental Icterohemorrhagic Spirochetosis in Young Goats.**

*Giorgio Ghetti, Ann. d'igiene, Rome, 32:513, June, 1922.*

Kids have hitherto been reputed to be refractory to ictero-hemorrhagic spirochetosis.

The writer, having taken up the study of the question anew and believing that this refractoriness was solely apparent and due to the methods hitherto employed for the introduction of the virus, took 4 kids about 3 months old, and inoculated 2 of these with subcutaneous and intraperitoneal injections and the other 2 with injections into the respiratory passage (intratracheal inoculation). After these last animals, previously shorn, were inoculated, he applied frictions with ice for 10 minutes to the thoracic walls, attempting, by this local refrigeration, to modify in their metabolism and functional extrinsication and consequently in their powers of defense, the ciliated epithelium enveloping the bronchi, and the epithelium of the alveoli, not forgetting, however, that the general organic resistance was also being reduced by this means. Three inoculations were made: the first 2 at an interval of 24 hours, the third on the fourth day.

While the kids that had received the subcutaneous and intraperitoneal injections presented no manifestations whatever and apparently remained in perfect health, the other 2 inoculated through the respiratory passage presented a clinical picture corresponding to that of benign human ictero-hemorrhagic spirochetosis. The ultra-microscopical examination of the blood and urine revealed the spirochete of Inada and Ido.

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(1d—127)

(1d—127)

**The Utilization of Peptone as a Source of Carbon by Citromyces.**

*Wl. Butkewitsch, Biochem. Ztschr., Berlin, 129:455, May 23, 1922.*

Experiments were undertaken with citromyces cultures on peptone analogous to those with aspergillus. The amount of free nitrogen in the form of ammonia in their cultures on peptone reaches 75% of the peptone's total nitrogen. This peculiarity is related, both in citromyces and in *Aspergillus niger*, to the accumulation of the acid combining with

ammonia. In the peptone cultures, not citric acid, as might be expected from Mase's assumption of the proteolytic origin of this acid, but oxalic acid is formed. The indications obtained for citromyces are wholly analogous to those determined for *A. niger*, in respect to (1) the quantitative proportions between ammonia formed in cultures on peptone and oxalic acid, (2) the relation of ammonia formation to mycelian development, and (3) the dependence of the value of the ammonification productivity of fungous surfaces ( $\text{NH}_3\text{—N}$ ) upon duration of culture and upon temperature.

Here, too, the proportion between oxalic acid and ammonia is somewhat less than with neutral ammonium oxalate. The relative oxalic acid deficiency in percentages of the total mass is expressed by values fluctuating between 16-19 for *C. glaber* and between 12-14 for *C. citricus*. In 15 and 30 day cultures of *C. glaber*, ammonia amounted in the first 15 days to 90-95% of the total ammonia accumulating in the entire 30 day period. The proportion of fungous growth to ammoniacal nitrogen reaches nearly 2.5 in the 15 day culture at 20° C. and diminishes to 1 as the culture ages to 30 days, and as temperature increases to 30° C. Alterations of the proportion show regular gradation in relation to the alterations in cultural conditions.

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(1d—128)

(1d—128)

#### **Formation and Accumulation of Oxalic Acid in Citromyces Cultures on Salts of Organic Acids.**

*Wl. Butkewitsch, Biochem. Ztschr., Berlin, 129-464, May 23, 1922.*

As the citromyces species are able to form and to accumulate oxalic acid in their development on peptone, the manifestation of this capacity on other carbon sources was searched for. It was found that oxalic acid is formed in the utilization by the citromyces of salts of organic acids as the carbon source, in which process the consumed acid is replaced in the salts employed for the cultures, the same as with *Aspergillus niger*. The reaction of the liquid in the citromyces cultures, on salts of organic acids, is slightly alkaline with litmus and remains acid with phenolphthalein. Fungus development and accumulation of oxalic acid is better on sodium salts than on ammonium salts and the acidity of the nutrient solution (on phenolphthalein) remains higher (3-2.5) in cultures of the latter salts than in those of the former (0.8-0.2).

*Aspergillus niger* possesses a greater capacity for accumulating oxalic acid than the citromyces. Its behavior toward the salts of tartaric acid shows particularly strong divergence. *Aspergillus niger* consumes this acid comparatively rapidly and completely, whereupon it is replaced by oxalic acid. But in citromyces cultures on tartrates, oxalic acid is present only in traces or is entirely absent. On salts of other experimental acids (citric, succinic, quinic) the citromyces were found capable of accumulating more or less considerable amounts of oxalic acid. The capacity was highest on salts of quinic acid which were entirely replaced by oxalic acid in a comparatively brief period (110 days). Altogether the sodium salt of quinic acid proved itself a particularly suitable carbon source for oxalic acid accumulation. On this salt the accumulation of oxalic acid in considerable amounts (besides carbonate) in

*Penicillium glaucum* cultures has been demonstrated. On salts of the other organic acids (tartaric, citric) only carbonate has been detected in its cultures. The same phenomenon has been determined also in *Aspergillus oryzae* and partly in *Mucor stolonifer*, in whose cultures with sodium salts of some organic acids carbonate also accumulated and a strong alkaline reaction developed. For fungi not capable of withstanding a highly alkaline medium, to which the citromyces as well as *Aspergillus niger* belong, the capability of accumulating oxalic acid in their development on salts of organic acids, appears as an advantageous peculiarity which restricts the increase of alkalinity in the consumption of organic acids.

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(1d—129)

(1d—129)

**Experiments with *Saccharomyces Marxianus* and Surface-Yeast R.**

*H. von Euler and Karl Josephson, Ztschr. f. physiol. Chem., Berlin, 120:43, June 1, 1922.*

Fermentation was followed volumetrically in 2 yeast strains, the carbon dioxide formed being led, during shaking, through capillary tubes into finely graduated burets and measured in the same at the natural degree of humidity, at room temperature and under atmospheric pressure. The fermentation flasks received 4% hexose and 2%  $\text{PO}_4$ . Acidity pH 4.5. Semifermentation time was indicated by the time in minutes in which one-half of the theoretically possible carbon dioxide was liberated at the definite temperature under the indicated conditions. In addition, the inversion velocity and the inverting capacity were determined or calculated. Further, the cell number was estimated with Thoma's counting-cell. The experiments were conducted with *Saccharomyces marxianus* and with surface yeast. It was found that the inverting capacity determined for *Saccharomyces marxianus*, which is very slight in comparison to that of ordinary culture yeasts and to the fermentative capacity, recalls the behavior of bottom yeast toward maltose. Fresh yeast ferments maltose approximately as quickly as glucose, but hydrolysis does not proceed more quickly than fermentation.

As regards splitting of sugar by *Saccharomyces marxianus*, this yeast is to be ranged with yeasts poor in free saccharase of which *Monilia candida* has hitherto been the typical example. In regard to the question as to whether there should be direct fermentation of maltose or preceding hydrolysis, that depends on whether the current procedure enables the totality of the maltase groups in yeast to be determined. *Saccharomyces marxianus* undergoes increase of cell number nearly as quickly in maltose-containing nutrient solution as in glucose solution in spite of the difference in the fermentability of the 2 sugar species by this yeast. As the assimilated carbohydrate amounts are extremely small, possibly that small amount may after all be actually hydrolyzed before assimilation. But in case the nutrient solution's carbohydrate does not serve directly as a source of energy by its fermentation, there might take place absorption without cleavage under transposition and polymerization to glycogen, which is formed from numerous substances and is stored rapidly.

(1d—130)

(1d—130)

**A New Madagascar Sporotrichum, *Sporotrichum Carougeui* Langeron 1913.**

*Maurice Langeron, Bull. Soc. de path. exot., Paris, 15:453, June 14, 1922.*

Pathogenic forms, other than the one named in the title, heretofore considered as *Sporotrichum*, properly belong to the genus *Rhinocladium*, Saccardo and Marchal, 1885, syn. *S. Link*. The form occurring in abscess and gumma formations accompanying tuberculosis in a child, as described by Fontoynt and Carougeau, is the only truly pathogenic sporotrichum. Cultures remain white, grow on all the usual media and are at first moist. When the conidia become abundant, the surface dries and becomes powdery, and more clearly white. Fungi must be differentiated microscopically. The new sporotrichum possesses a septate mycelium of large diameter (2.5-4 microns). The conidia are given off at all points of the mycelial segments, and the various conidia may form subsidiary buds. *Sporotrichum* is distinguished chiefly by its characteristic conidial structure. Yeast forms occur almost solely in lesions, never in cultures, in which the typical mycelium and conidia develop. The yeast forms of *S. carougeui* may appear in cultures under conditions not yet fully defined. Both conidial and yeast forms probably exist in the tissues.

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(1d—131)

(1d—131)

**Hormodendron Fontoynti Langeron 1913, Cause of the Parasitic Achromia of Madagascar.**

*Maurice Langeron, Bull. Soc. de path. exot., Paris, 15:436, June 14, 1922.*

This genus belongs to Dematia. The spores, rarely septate, are united in chains originating from the extremity of the conidiophore or its branches. *Hormodendron* appears to be a conidial form of *Cladosporium herbarum*. Both terms may be retained, the 2 forms being thus named separately. The conidial, or hormodendron, character always appeared in cellular cultures, on carrot or in sugar gelose. Under high power, the terminations of the conidiophores are found to bear tubercles, whose surface is thickened at points where blastospores are inserted. The latter are very easily detached. Sometimes chains of blastospores originate from tubercles, sometimes the terminations of the conidiophores produce blastospores giving rise to chains of conidia. A beautiful branching mycelium is thus produced, a dust composed of spores occurring on the slightest contact.

The spores are characteristic, oval, elongated, and with or without septa; there may be 1-3 septa. The membrane is thick and double, and reinforced at the junction of spore and mycelium. The spores may be terminal or interpolated. The fungus does not vegetate at 37°, dies very soon at ordinary temperatures and, to be kept alive, must be reinoculated at least every 2 weeks. The width of the mycelium varies from 2.5-7.8 microns; the segments are about 21 microns long. The blastospore chains range from 5x3 to 8x4 microns. The cultures are downy, at first white, then becoming dark green.



(1d—132)

(1d—132)

**Correlation of the Life Cycle of a Parasite with the Metamorphosis of Its Host.**

*Nadine Nowlin, J. Parasitol., 8:153, June, 1922.*

In the fly, *Sciara coprophila*, a new host has been found for a gregarine previously noted only in *Sciara nitidicollis*. It is the fourth species recorded in the rare genus *Schneideria* Léger, and the only one found outside of France. A table is given showing the characteristics of this specimen, *Schneideria mucronata* and *Sciara coronata*. The specimen is without doubt neither one of the 2 species, but is a new species which Nowlin called *Sciara metamorphosa* because of the close correlation of its life cycle with the metamorphosis of its host. It differs from the other recorded species in that (a) its intracellular phase is polycystid; (b) the epimerite is never functional; and (c) both epimerite and protomerite are shed before the gregarine leaves the cell.

It begins its life cycle as an intracellular parasite in the midgut of the fly *S. coprophila*. Here it undergoes a polycystid development, possessing an epimerite, a protomerite and a deutomerite. While still inside the cell all divisions atrophy except the deutomerite, and the parasite emerges a monocystid. In the larva the gregarine goes no farther than the sporont stage. In the pupa, sporonts, solitary up to this time, unite in twos, head to head, shorten into spheres and begin segmentation, meanwhile laying down a cyst wall. In the adult fly the formation of the spores is completed and the spore chromatin divides preliminary to the production of sporozoites.

Each of the 3 phases of the host's development is linked with a definite and limited phase of the parasite's development. The correlation is both physiologic and morphologic; the parasite and host feed and grow at the same time; have their quiescent periods at the same time, and carry on the propagation program simultaneously. The author suspects that this extraordinary adaptation of the parasite's life cycle to fit that of its host, may be frequent in the gregarine group and may explain the incompleteness of so many gregarine life histories.

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(1d—133)

(1d—133)

**Some Observations on the Effect of Quinin upon the Growth of Malaria Plasmodia in Vitro.**

*C. C. Bass, Am. J. Trop. Med., 2:289, July, 1922.*

A concentrated (15%) stock solution of quinin dihydrochlorid in 0.85% sodium chlorid solution was prepared. The desired amount of quinin was added to the blood containing plasmodia by means of very small measuring pipettes. The blood was obtained from a patient who had a very heavy *Plasmodium falciparum* infection and had not taken any quinin. Blood (10 c.c.) was drawn from the median basilic vein in the usual way, 0.5% of dextrose (in 50% solution) was added and the blood was defibrinated for cultivation for malarial plasmodia. This blood containing plasmodia was used in 3 experiments, by which it was indicated that some of the quinin is held in solution by the serum and that it is not all quickly taken up by the blood cells or removed from the serum; also that more quinin is taken up and held by the cells than by

the serum; and that quinin in the blood is taken up within a period of 20 minutes by the cells, or by the plasmodia to sufficient extent to prevent their growth and finally to kill the plasmodia.

The little information obtained, although not conclusive, indicates that quinin in therapeutic proportions prevents the growth of malaria plasmodia in vitro, and in fact kills them.

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(1d—134)

(1d—134)

**The Staining of Thick Drops of Blood (Thick Films) for the Study of Malarial Parasites.**

*Guido Bini, Policlinico (Pract. Sect.), Rome, '29:913, July 10, 1922.*

The writer describes a particular technic of his own for staining preparations of blood in thick drops. Having found the method recently indicated by Schilling unsatisfactory, because the early forms of parasites (the tertian and estivo-autumnal spirilla) are not stained with sufficient distinctness, he tried a method without fixation, one which is more rapid and in which he could utilize a technic of double staining with which he had experimented since 1920.

The technic consists in: (a) placing the blood on slides perfectly cleaned (3-4 drops of blood mixed by means of the needle that served to make the puncture), defibrinating and spreading it so as to obtain a uniform disk about 1 cm. in diameter; (b) drying the smears in a horizontal position for not less than 2 hours; (c) placing the slides on horizontal supports made with small parallel glass rods raised above the table. Each slide is covered with an aqueous solution of Giemsa's stain in the proportion of 1 drop of the stain to each cubic centimeter of distilled water. This stain-hemolysis lasts for 2 to 3 minutes, i. e. until the hemoglobin rises like a cloud from the slide; (d) lateral washing of the slide, which, remaining in a horizontal position, is covered for 6-8 minutes with an aqueous solution of Leishman's stain (1 drop of the mother-solution for each cubic centimeter of water); (e) lateral washing of the slide by a gentle spraying of distilled water, so that the water trickles over the blood smear, drying in the air in a vertical position.

The preparations are then examined by the immersion lens. All the parasitic forms appear distinctly with their structural peculiarities, the chromatin being stained a brilliant ruby red, the protoplasm blue: the pigment which, as is well known, has various forms and groupings according to the parasitic type, degree of maturation, and cycle (asexual or gametic), is more evident than in fixed preparations, since the basis of the preparation is entirely colorless: the leukocytes, the platelets, and the parasites alone remain.

Having employed this technic upon a large scale, the writer is able to affirm that in certain preparations of ordinary tertian malarial blood (*Plasmodium vivax*), and especially in the earlier phases of the parasite, the erythrocyte that has been attacked by the parasite is preserved, unlike the normal ones which disappear completely. It is shown with its distinct outline, of a pale rose-color and filamentous structure. The granules of Schüffner are often visible. The writer has been able to make these affirmations only with regard to the tertian forms (owing

to the period in which these researches were begun, i. e. the preëpidemic period during which the forms were almost exclusively these); he did not observe similar results in the rare cases of estivo-autumnal forms that came under his observation. He also noted that the red corpuscles with basophile granulations, unlike the normal, resisted the process of hemolysis, persisting as disks with indefinite contours and a trabecular structure composed of very fine granules of light blue color.

He considers that the above described method of staining has certain advantages and, confronting it with smears taken contemporaneously and with a material consisting of some hundred preparations, he arrives at the following deductions:

(1) 10% of the blood which gave negative results with the smear, gave positive results with the thick films;

(2) To discover the parasites in the thick films requires only one-sixth of the time necessary to detect them in the streak films. The preparations are not fixed, a detail which has little interest in diagnostic verifications on a large scale; but even so, the writer asserts that these stained preparations are in an excellent state of preservation at the end of over 2 months.

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#### **Atypical Forms of Plasmodium Praecox.**

*Pierre Hornus, Arch. d. Inst. Pasteur de l'Afrique du Nord, Tunis, 2:227, April-June, 1922.*

The author reports the occurrence of the forms of *Plasmodium praecox* noted by Viallate, and new forms, in cases of terminal, unrecognized malaria where the patient dies without treatment by quinin. He thinks that these forms are usually present in deep structures, occurring in the peripheral vessels only when the bodily resistance is much weakened in patients gravely ill and untreated by quinin. In an early stage of development, the new form shows an increase in size, chiefly at the pole opposite the chromatin. The parasite is ameboid, and may appear in various forms, and the chromatin may divide and collect at the 2 extremities of the parasite. In a more advanced stage, the parasite is asymmetrically enlarged, but less mobile. The chromatin assumes various forms, but no pigment appears. In a following stage, the parasite is rounded, regular, occupies a quarter of the red cell and has a single, distinct pigment granule at its center, replacing the nutritive vacuole and chromatin, which have disappeared. Rosette forms also occur. The occurrence of these forms in the peripheral vessels is a grave sign and an urgent indication for the immediate use of quinin.

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#### **A Study of the Escape of Cercariae from Their Snail Hosts.**

*William W. Cort, J. Parasitol., 8:177, June, 1922.*

Cort undertook a series of experiments on the escape of cercariae from their snail hosts to determine the numbers of cercariae escaping from snails infested with trematodes and the times at which these cercariae made their escape. The following cercariae were studied: (1) *Cercaria elephantis* Cort from *Planorbis trivolis* Say; (2) *Cercaria*

emarginatae Cort from *Lymnaea emarginata angulata* Sowerby; (3) an undetermined echinostome cercaria from *Physa ancillaria parkeri* Currier; (4) an undetermined stylet cercaria from the same host. The method of determining which snails were infected was by placing 100 snails in groups of fours and fives in bottles one-third full of water and examining the water for cercariae. If the water was positive, the groups of snails were further divided, only one snail being placed in a bottle and by further examinations the individual snails infested were determined.

A series of tables show the results of these experiments. The number of cercariae escaping from snails of *P. trivolis* was very large, but when the records of the escape from their snail hosts of the other 3 species of cercariae studied are examined, the numbers involved are even more striking, e. g. in the case of a snail of the stylet cercaria series over 3000 cercariae escaped on one day, and in the *C. emarginatae* series over 5000 escaped on one day. These findings emphasize the enormous reproductive wastage in the development of the cercariae in the digenetic trematodes, which is necessary on account of the great difficulty that they experience in reaching their final hosts. There is a considerable variation in the escape of cercariae from different snails in the same species and even from the same snail. It is further possible to correlate the numbers of cercariae given off from any snail with the numbers of sporocysts in its liver. The temperature of the environment seems to very significantly affect the numbers of cercariae escaping from the snails, for on a cold and rainy day only 281 are recorded and for the same snail on warmer days 1000 and 2000 cercariae escaped. Judged from these findings, it may well be that the infectivity to man of water in which live snails that harbor cercariae of the human schistosomes, may be found to be profoundly influenced by temperature.

Cort found that the escape of the cercariae did not extend over the whole 24 hours, but that there were periods when they escaped in numbers followed by periods during which none escaped, i. e. the escape came in waves. Perhaps the most surprising finding was that the time of these waves differed in different snails, in some occurring in the daytime and in others at night. Also the time of these waves suffered but slight change on the different days on which a given snail was studied. In the echinostome species the escape of the cercariae was almost entirely limited to the daytime, showing a very striking positive reaction to daylight. The stylet form studied escaped from its small host during the whole 24 hours, although there was a distinctly smaller number which escaped during the night than during the day.

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(1d—137)

(1d—137)

#### **The Development of *Fasciolopsis Buski* Lankester.**

*Koan Nakagawa, J. Parasitol., 8:161, June, 1922.*

*Fasciolopsis buski* is an important human parasite which has been reported in China, India, Bornea, Sumatra, Cochin China and Tonkin. The writer obtained *F. buski* from native pigs in Formosa which measured 25-40 mm. in length and 10-17 mm. in width; eggs from these were incubated and free swimming miracidia obtained. The time required for the development of the miracidium varies a little according

to the season of the year. In the summer it generally takes 2-3 weeks. Nakagawa was able to prove experimentally that 2 species of snails, *Planorbis coenosus* Benson and *Segmentina largillierti* Dkr. could serve as the intermediate hosts of *F. buski*. When these species were placed in water containing numerous actively swimming miracidia, the miracidia penetrated into the snails. At this time they threw off their coats of cilia. After penetration they became rounded and immobile, and after losing the digestive tract, are changed into mother sporocysts. These sporocysts gradually increase in size, the embryonic cells enter into cleavage and gradually rediae become recognizable within the sporocytes. The rediae when germ cells become visible escape from the sporocytes and moving actively penetrate the walls of the alimentary canal, respiratory cavity and liver of the snail. As time goes on the rediae increase in size and inside of them cercariae develop. In some of the rediae, however, a new generation of rediae develop. The mature cercaria while still within the redia measures about 0.23 mm. in length and about 0.23 mm. in width; it has a long tail, and the body is full of cytogenous glands which give it a dark appearance. As the cercariae become mature they escape from the redia and swim freely. The most characteristic feature of the cercaria is the conspicuous limbs of the excretory bladder situated along the sides of the body and filled with coarse granules. The encysted cercariae, which also have this same characteristic, are found attached to water plants. By feeding pigs and dogs with the encysted cercariae, Nakagawa obtained immature forms and sexually mature adults from the small intestines. The life cycle of *F. buski* as well as its mode of infection furnishes data for the prevention and control of the disease which this parasite produces in man. Accompanying the descriptive material are a number of very interesting figures showing the stages in the development of *F. buski*.

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**A Critique of the Supposed Rodent Origin of Human Giardiasis.**

*Charles E. Simon, Am. J. Hyg., 2:406, July, 1922.*

The objects of this investigation were to determine (1) whether *Giardia* which is found in man is morphologically identical with the form or forms which occur in the common house mouse, the Norway rat and certain types of field mice; (2) to ascertain whether the various types of *Giardia* are nonspecific for their hosts; (3) if host specificity does not exist, whether a given type after transference from its usual host to a host of a different species retains its original morphologic characteristics.

With the exception of the parabasal body no essential structural differences exist between the mouse form and the human type, and apparent differences are merely the expression of stages in the life history or development of organisms. A comparative study of the measurements showed that the values which were obtained for the rates of length and breadth reveal an entirely different size ratio between the human and mouse type and also a somewhat different type of distribution. The 2 types of cysts can be readily differentiated morphologically, the essential factor being the appearance of coarse chromidial



masses in the cytoplasm of the mouse type, which are either never seen in the human type, or if something suggestive of these masses appears, there is so little of it that it would scarcely attract attention. Experimental feeding showed the culture rats and wild rats negative for the human type but positive for the mouse form. Simons concludes that the human form must be destroyed by the gastric juices of these animals. These feeding experiments thus support the conclusion that human giardiasis is not of rodent origin, so far as the mouse type is concerned; that the mouse type, as well as the human type, constitute separate species.

The most important difference between the *Giardia* of the human type and that of the meadow mouse is that of size. There is not only a material difference in mean length but also an entirely different type distribution. Feeding experiments show that culture rats and wild rats cannot be infected with *G. microti*. On the basis of these morphologic, biometric and experimental studies, the author believes to have established that specific differences exist between the human *Giardia* and the mouse form, as was first suggested by Bensen, and that similar differences also exist between the human form and the meadow mouse form and between the latter and the mouse form. Therefore, he accepts the name *muris* for the mouse form, and *microti* for the meadow mouse form. For the human form he believes that the organism should henceforth be known as *Giardia lamblia*.

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**The Systematic Relationship of *Giardia Lamblia* Stiles, 1915, from Man and *Giardia Agilis* Kunstler, 1882, from the Tadpole.**

*Robert W. Hegner, Am. J. Hyg., 2:435, July, 1922.*

The objects of this contribution are to furnish a modern description with figures and measurements of *Giardia agilis* from the tadpole, which may be used to determine the systematic relationship of this species and *Giardia lamblia* from man, and to record certain variations in the size of specimens of *G. agilis* from different tadpole hosts. *G. agilis* may be described as a long, slender species with the general characteristics of the genus. The range in length was found to be from 14.4-28.9 microns, and in width from 2.6-5.1 microns. A diagram is given which clearly shows the differences in this species and that of the mouse, meadow mouse and man. The structures and organs of this species are described in detail; the most distinguishing feature seems to be the nuclei which are much larger in proportion to the size of the sucking cup than those of any other species of *Giardia* yet described. A table is given which shows that specimens of *G. agilis* from different tadpoles sometimes exhibit uniform differences in size. These differences may be due to the presence of heritably diverse races, as regards size, or to changes brought about by the different environmental conditions within the intestines of their tadpole hosts.

Kunstler and Gineste described a second species of *Giardia* from tadpoles which they called *G. alata*. Hegner and others believe that this is the same species as *G. agilis* and if there is only one species in the tadpole the laws of nomenclature give *G. agilis* priority. This form is

similar in structural characteristics to *G. lamblia* from man, and the differences in size and shape between the 2 species are not sufficient to place them in separate genera or subgenera.

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(1d—140)

**A Comparative Study of the Giardias Living in Man, Rabbit and Dog.**

*Robert W. Hegner, Am. J. Hyg., 2:442, July, 1922.*

Hegner made this study in order to determine more accurately than has been done heretofore the structural characteristics and size of Giardias found in rabbits and dogs. Tables of measurements and cuts of both types are given. *Giardia duodenalis* Davaine, 1875, found in rabbits is characterized by a narrowing of the anterior region, as seen in front view, and a broadening across the center of the lateral shields, by a comparatively long "tail" and by 2 long bent "parabasal bodies." It is both broader and longer than the *G. lamblia* from man, but the difference in the ratio of body length to body breadth shows that the latter is more slender than *G. duodenalis*. This work confirms that of Bensen's.

Giardias have not been reported very often in dogs. Hegner proposes the name *G. canis* sp. nov. for this *Giardia*. The trophozoite differs from that of *G. lamblia* from man and *G. duodenalis* from the rabbit principally in size, shape, and the form of the "parabasal bodies." The anterior end of the trophozoite in front view is broader than in the other 2 species; the diameter across the center of the lateral shields is less than in *G. duodenalis*; the 2 "parabasal bodies" are longer than the parabasals of *G. lamblia*, but shorter than those of *G. duodenalis*; and the "tail" is shorter than in *D. duodenalis*, but about the same relative length as in *G. lamblia*. The cysts of *G. canis* are of the same shape as those of *G. lamblia*, but slightly larger both in length and breadth. This data conclusively proves that each animal is infected with a separate species of *Giardia*.

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(1d—141)

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**A New Genus of Metchnikovellidae.**

*V. A. Dogiel, Ann. de l'Inst. Pasteur, Paris, 36:574, July, 1922.*

The author describes an organism parasitic in a species of *Selenidium* attached to the intestinal wall of the annelid *Travisia forbesi*. The parasite was in the cystic stage, and bottle-shaped. The cyst wall was thick and double. Each cyst contained 8 to 12 spores. Thin-walled, transparent cysts, with indistinctly differentiated spores, were also observed. The poles of this genus are unlike. The narrow, bottle-like opening, closed by local thickening of the wall, probably allows the spores to escape. The author proposes the name *Caulleryetta mesnili* for this parasite.

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(1d—142)

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**Studies on the Notocotyles.**

*C. Joyeux, Bull. Soc. de path. exot., Paris, 15:331, May 10, 1922.*

The notocotyles are trematodes provided with a single sucker, and living chiefly in the avian cecum. The author found a new species in the

water rat, *Arvicola amphibius* L., for which he proposes the name *Notocotylus noyeri* n. sp. It was 2 to 3 mm. long and 1 mm. wide, oval and basin-shaped, narrow anteriorly. The color was whitish. The genital structures were visible with a hand-lens. No spines were found on the surface, but they may have been detached in the preserving liquid. The typical papillas were present ventrally, arranged in 3 rows of 15 each, most being invaginated. The buccal sucker was 230 microns in diameter and the rounded testicles, clearly visible, about 300 microns in diameter. The female vagina, uterus, eggs and other structures were distinct. The new species differs clearly from 4 avian, and another rodent, parasite.

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(1d—143)

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**Notes on Mosquitoes and Other Blood-Sucking Flies from Porto Rico.**

*Francis Metcalf Root, Am. J. Hyg., 2:394, July, 1922.*

Root gives a list of blood-sucking flies previously reported from Porto Rico. All of his collecting was carried on in the narrow coastal plain which surrounds the island. The principal collecting points were Rio Piedras and Martin Pena, near the capital, on the rainy north coast, and the central Aguirre, a large sugar plantation between Guayama and Salinas, on the dry south coast. The habitat, form, color, etc., of about 18 species obtained are described in detail.

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(1d—144)

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**The Larvas of American Anopheles Mosquitoes, in Relation to Classification and Identification.**

*Francis Metcalf Root, Am. J. Hyg., 2:379, July, 1922.*

The author describes extensively the larval characters which are useful in distinguishing between different species of *Anopheles*, indicates the groups into which the species fall, and gives descriptions of these characters for the species which have been examined. The characters which are of use in discriminating between the different *anopheles* larvas are almost entirely the variations in form and position of certain hairs or modifications of hairs, viz. the dorsal head hairs, dorsal thoracic hairs and abdominal hairs and their groups. For the convenience of field workers, a key or synopsis to the American *Anopheles* larvas is given, so far as they are known. Numerous cuts are given showing the form and position of the various groups of hairs.

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(1d—145)

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**A New Dutch-Indian Anopheline.**

*N. H. Swellengrebel, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:443, July 29, 1922.*

*Bironella gracilis* Theobald is a small, dark anopheline with unspotted wings; the first bifurcation of the wings is very short; the palps of the female are 0.6 the length of the proboscis. The male genitals include 2 hooks at the site of the harpagons. The larvas have

2 pairs of fanlike processes on the thorax. This form differs from the other members of the species by the structure of the wings and of the male genitals. If the larvas were not typical, doubt might exist as to whether or not this insect actually belonged to the genus *Anopheles*. Specimens were observed for the first time in New Guinea in January, 1921.

(1d—146)

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**Observations on the Development of *Heterakis Papillosa* Bloch in the Chicken.**

*Cesar Uribe, J. Parasitol., 8:167, June, 1922.*

Graybill published in 1921, an article on the development of *Heterakis papillosa* in the fowl. The result of Uribe's experiments confirm for the most part the observations of this writer. For instance, Uribe found on the walls of the mouth cavity and near the oral aperture 3 distinct teeth, and at the bottom 3 other very small teeth were seen, projecting vertically, toward the oral aperture. Also, the anterior portion of the esophagus, as well as part of the oral cavity, is surrounded by a thickening of the muscular tube, thus forming a definite pharyngeal bulb. The excretory pore is found in the anterior third of the body, slightly posterior to the middle point of the esophagus. Travassos (1913) described the spicules, for the same species studied in Brazil, as being equal and only 0.27 mm. long. The spicules in Uribe's specimens are not only unequal in size, one being about 3 times as long as the other, but they are quite different in shape. The shorter one, 650 microns, shows 2 lateral flanges and a characteristic twist of its tip, while the longer one, 2 mm., has only a single flange and shows a uniform curvature.

The development of the egg outside the host is greatly influenced by environment and it is apparently very resistant to unfavorable influences. The results obtained with respect to the resistance of *Heterakis* ova to drying and to variation of temperature for the most part confirm those of Graybill. The nonembryonated eggs in some cases are promptly destroyed by phenol, hydrochloric, sulphuric and acetic acids in varying strengths; in other cases they showed vacuolization of their contents after 2 weeks of exposure; or they did not develop at all. The fact that they developed uninjured in 1.5% nitric acid, which renders the material external to the shell of the egg bacteriologically sterile, may be of value in determining the source of the protozoön of blackhead.

The development of the larva and the habitat and pathology of *Heterakis* are briefly given. It hatches in the intestine of the fowl and undergoes its entire development in the cecum. This species requires a considerable period of time to mature, although growth is accelerated after each moult. In the cecal discharge, eggs and occasionally dead females are found. Such eggs when sufficiently incubated and ingested by a suitable host produce heavy infestation. The adult stage is also passed in the cecum. The structure of the mouth with definite teeth suggests the possibility of attachment and utilization of tissue fluids as food—such fluids being either the cecal contents, or, as in one instance, the blood of the hen.

In a series of chickens that were not killed until 20 days after the

ingestion of *Heterakis* ova a large proportion showed a marked typhlitis. However no protozoa were demonstrable in any of the lesions. A chicken of another series, killed on the thirteenth day, showed black-head with typical lesions of both liver and cecum. It is not known whether *Heterakis* produces greater injury in the cecum of the turkey or the chicken.

## 1e. IMMUNOLOGY, SEROLOGY AND HEMATOLOGY

(1e—117)

(1e—117)

### Investigations on Protective Ferments.

*Gustav Blunck, Münch. med. Wchnschr.*, 69:1005, July 7, 1922.

Abderhalden himself tried to use stained substrates for the demonstration of protective ferments, analogously to the demonstration of pepsin (Grützner) with carmin fibrin, but all the tried stains proved to be not serum-fast. The author found in metachrome violet B a stain absolutely serum-fast, and also otherwise appropriate. Under exactly similar conditions as for the staining of the substrate, the amount of catabolic ferment in the serum can be determined quantitatively and colorimetrically. In carcinoma, only the carcinoma cells and not the cells of the unchanged mother tissue were decolorized. The specificity extends so far that the serum of carcinoma patients decomposes only carcinomas of a similar mother tissue. The author showed similar effects of the autolytic and of the protective ferments and therefore assumes them to be identical. The question, whether the ferments under discussion arise in the blood and are only increased in the organs—they would then be true protective ferments—or whether they arise in the organs as autolytic ferments, has both a theoretic and also a practical significance. In plants, catabolic ferments are also demonstrable, as for example against gall and so-called vegetable cancer. The substrate was derived from these particular parts of the plant washed free of chlorophyll; and the coloring was done with diamin black HB; the fresh, press juice was immediately centrifugalized and used as plant serum, but nevertheless there were frequent errors from impurities.

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(1e—118)

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### The Influence of Atropin and Pilocarpin on Antibody Formation in Rabbits.

*Georg Joachimoglu and Yoshitsune Wada, Arch. f. exper. Path. u. Pharmacol., Leipsic*, 93:269, June 23, 1922.

Experiments were carried out on rabbits immunized with typhoid bacilli intravenously. Varying single doses of atropin and pilocarpin were given intravenously or subcutaneously and agglutination tested before and 2 hours after injection, or the alkaloids were administered in smaller doses daily. Results showed that no regular and distinct influence on agglutinin formation of atropin or pilocarpin was determinable. Pilocarpin produced absolutely no increase of agglutinins, while chronic atropin medication frequently diminished agglutinin formation.



(1e—119)

(1e—119)

**Vaccination of the Guinea-Pig Against Anthracic Blood.**

*A. Besredka and Y. de Trévisé, Ann. de l'Inst. Pasteur, Paris, 36:562, July, 1922.*

Anti-anthrax serum derived from horses and similar animals protects the guinea-pig against only a very small lethal dose of virus, and this protection is not very sure. All laboratory animals are difficult to vaccinate against anthrax. The latter attacks only the skin of the guinea-pig. Immunity to anthrax does not correspond with that opposing other bacteria. Vaccinated animals sometimes die from inoculations with anthracic blood. Possibly the phagocytes are paralyzed by substances derived from the bacterial capsule. The skin of the guinea-pig may be rendered immune to anthrax.

Blood was obtained from the hearts of guinea-pigs inoculated subcutaneously with 0.1 to 0.01 bouillon culture 24 hours old. When 0.01 to 0.02 drop of such blood was injected under the skin of a new guinea-pig, it caused death. It was employed in tests with unvaccinated guinea-pigs and with those whose skin had been rendered immune by vaccination. Subcutaneous injections of 4 drops of the virulent blood, or 200 times the dose lethal for unvaccinated animals, were borne with no difficulty by the immunized animals. Cutivaccination thus solidly immunizes the guinea-pig to anthracic blood.

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(1e—120)

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**The Conjunctival Inoculation of Anthrax.**

*Marguerite Aïtoff, Ann. de l'Inst. Pasteur, Paris, 36:567, July, 1922.*

The author has tested white mice, rats, guinea-pigs and rabbits. Gelose cultures, 24 hours old, forming a thick emulsion with a little normal saline, were placed upon the conjunctivas. The lids were held closed for a few moments, then released and the escaping liquid wiped off. Anthrax bacteria could be recovered from the conjunctival sac for 24 hours to 7 days, usually disappearing in 2 or 3 days. Cultures were similarly inoculated into the conjunctiva of a guinea-pig affected with traumatic conjunctivitis and corneal ulcer. Blood taken from the heart of a guinea-pig dying of anthrax was inoculated into the conjunctivas of guinea-pigs and white mice. Leukocytic action was abolished in some of the tests by first placing a 1% solution of ethocain in the conjunctiva. None of these tests were fatal except in inoculations with infected blood. Here 2 of 8 guinea-pigs died. The conjunctiva is therefore practically invulnerable to virulent anthrax bacilli, partly, perhaps, because of the mechanical conditions. There is also a natural local immunity.

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(1e—121)

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**Active Immunity to Diphtheria in the Absence of Detectable Antitoxin.**

*A. T. Glenny and K. Allen, J. Hyg., London, 21:100, June, 1922.*

By means of the intradermic method of testing the antitoxic content of a serum, it is possible to detect with certainty the presence of

such a small quantity as 1/2000 of a unit of antitoxin per c.c. Among a number of guinea-pigs and rabbits which had been used to test the antigenic value of toxin-antitoxin mixtures, several were found which had not responded to the injection of the primary stimulus by the production of even 1/2000 of a unit of antitoxin per cubic centimeter of blood. These animals on the injection of another toxin-antitoxin mixture showed by the rapid production of circulating antitoxin that the primary stimulus had induced a condition of active immunity, though a detectable amount of antitoxin was not present in the circulation. Further experiments show that the condition of active immunity continues after the disappearance of all circulating antitoxin produced by the animal in response to a previous stimulus.

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**The Schick Dose of Diphtheria Toxin as a Secondary Stimulus.**

*A. T. Glenny and K. Allen, J. Hyg., London, 21:104, June, 1922.*

From a series of experiments, the results of which are shown in 7 tables, the authors have demonstrated that the very small amount of toxin used for the Schick test, apart from its action as a diagnostic agent, may also play an active part in immunization, and that the small amount of diphtheria toxin or a fraction of a Schick dose may act as a secondary stimulus. This action may cause an animal to give a negative reaction when tested 7 days or more after the first positive reaction, as demonstrated in the case of 4 rabbits and 4 guinea-pigs. The experiments on 4 rabbits proved that the antigenic value of a Schick dose of toxin as a secondary stimulus may be as high as that of a reasonable dose of a toxin-antitoxin mixture suitable for human immunization. The antigenic value of a Schick dose as a secondary stimulus can be demonstrated in animals which have not produced a detectable quantity of antitoxin as the result of primary stimulus and in animals whose actively produced antitoxin has fallen below a detectable level.

In the case of 1 guinea-pig it was shown that a Schick dose of toxin which gives a positive reaction may, by acting as a secondary stimulus, produce a rapid increase in the antitoxic value of animals already containing some actively produced antitoxin; and further, a dose of toxin which causes no reaction may, by acting as a secondary stimulus, produce a rapid increase in the antitoxic value of animals already containing some actively produced antitoxin. A Schick dose of toxin may fail as a secondary stimulus if the antitoxic content at the time of injection is comparatively high.

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**Reaction of the Medium in the Production of Diphtheric Toxin.**

*G. Abt and G. Loiseau, Ann. de l'Inst. Pasteur, Paris, 36:535, July, 1922.*

For producing active diphtheric toxin, the exact reaction is less important than the quantity of carbohydrates, preparation of the peptone and condition of the meat. The Martin medium gives uniformly

satisfactory results, providing a toxin of which 0.0014 c.c. kills a 350 gm. guinea-pig in 4 days. The reaction of the medium ranges from pH of 7.5 to 7.9. Equally active toxins result with a reaction range of pH 6.8 to over 7.8. The fatal dose remains nearly the same from the seventh to the eleventh day of culture. Beyond a pH of 8.6 toxin does not appear to be formed and below 6.8 its activity is very low. With an initial pH of 5.8-6.1, 0.1 c.c. is required to kill the guinea-pig in 4 days. Distinctly acid or alkaline reactions unfavorably affect preservation of the toxin. A too acid initial reaction may become favorable in 2 or 3 days, but no toxin is formed.

In the Martin medium, the course of the reaction depends on whether the initial pH is above or below a range of 7.3 to 7.4. Acid media tend to alkalinity and conversely. The reaction curves nearly correspond in 4 days, somewhat sooner with very alkaline media. The Martin is prepared as follows: The meat consists of first quality veal from the hind quarter, very white and free from fat, tendon and aponeurosis. It is minced and placed in twice its weight of water (15-20 kg. meat to 30-40 liters water), the mixture being raised to about 37° C. and then incubated at 37° for about 20 hours. The floating meat is then skimmed off without pressing it. The liquid remaining constitutes the maceration employed.

To prepare the peptone solution, the stomachs of pigs, washed and fat-free, are minced; 200 gm. minced stomach are placed in 1 liter water heated to 50° C. and acidulated with 10 c.c. pure HCl. The mixture is digested, in porcelain vessels holding 25 to 30 liters liquid prepared in the proportions indicated, for 15-18 hours at 50°, then heated to 100° to destroy excess pepsin, and cooled. A 4% peptone solution is thus obtained. It is allowed to clarify by standing for 2 or 3 days, decanted, and is then ready for use.

To prepare the bouillon, the necessary quantity of peptone solution is neutralized, hot, with soda, tournesol paper serving as indicator. Large flakes separate and the filtered liquid gives a perfectly clear solution of peptone. Equal volumes of the veal maceration and the neutralized peptone solution are mixed, heated to 100° and strained through cloth. The filtered liquid is kept at 70-80° for making alkaline with soda solution. With phenolphthalein as indicator, the mixture is brought just to the turning point, a check tube being used for comparison with the faint pink color. The alkaline bouillon is filtered through Chardin paper, autoclaved at 120° for 30 minutes, filtered through ordinary paper and placed in Fernbach flasks, 1200 c.c. per flask. The flasks and contents are sterilized by heating for 30 minutes at 115°. Am. 8 diphtheric bacilli produce a very active toxin.

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#### **The Action of Diphtheria Toxin on Mice.**

*A. T. Glenny and K. Allen, J. Hyg., London, 21:96, June, 1922.*

It has been generally accepted that mice are almost insusceptible to diphtheria toxin. By using potent toxin, prepared by concentration (Glenny and Walpole, 1915) the writers were able to compare not only the minimal lethal dose for mice with that for guinea-pigs, but also to compare the neutralizing effect of antitoxin upon toxin in the 2 species

of animals. The m. l. d. for mice was determined by both intravenous and intramuscular injection. It was found that 0.05 c.c. can be taken as the intravenous m. l. d. for this toxin in mice, i. e. 60 times the subcutaneous m. l. d. for guinea-pigs, while the intramuscular m. l. d. was 0.08 c.c., i. e. 100 times the subcutaneous m. l. d. for guinea-pigs. To determine the neutralization value of antitoxin for toxin when injected intravenously into mice, 0.2 c.c. of toxin was taken as a test dose. It was found that antitoxin has the same neutralizing power for toxin in mice as in guinea-pigs.

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(1e—125)

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**Receptors of the X and Z Types of Bacilli.**

*E. Friedberger, Werner Zorn and Gertrud Meissner, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34:259, June 28, 1922.*

Repeated attempts at immunity reactions between the O and H forms of the strain  $X_{10}$  and rabbit immune serum, lead to these conclusions. Bacilli of the strain  $X_{10}$ , whether of the ordinary or of the O forms, after being charged with serum of typhus patients, are no longer able to abstract any agglutinin from rabbit immune serum; similarly, the same bacilli, charged with corresponding rabbit immune serum, do not affect the serum of patients. In like manner the  $Z_1$  strain of pyocyaneus bacilli (cultured from the blood of typhus patients), previously exposed to rabbit serum rendered immune to  $HX_2$ , do not abstract agglutinin from rabbit serum rendered immune to  $Z_1$ , nor do they abstract agglutinin from rabbit serum rendered immune to  $HX_2$  if previously exposed to  $Z_1$  immune serum.

The next attempts were made with  $X_{10}$  and  $Z_1$  on the serums of other animals. Experiments with serums of guinea-pigs gave the same results as with those of rabbits, i. e. guinea-pigs immunized with  $Z_1$  formed agglutinins only for the  $Z_1$  strain of bacilli, and guinea-pigs immunized against  $HX_{10}$  and  $OX_{10}$  formed agglutinins only for the corresponding strains of bacteria.

Experiments on fowl gave totally different results: Fowl immunized against  $HX_{10}$  formed agglutinins with  $HX_{10}$ ,  $OX_{10}$ ,  $HX_2$  and even  $Z_1$ ; similarly, following immunization against the  $OX_{10}$ , or  $HX_2$ , or  $Z_1$ , agglutinins were formed for all other strains of bacteria.

Corresponding experiments with immune serums gave the immunity reactions to be expected:  $OX_{10}$ ,  $HX_{10}$  and  $HX_2$  bacteria possess receptors also for  $Z_1$  and, conversely, the  $Z_1$  type of bacteria possesses receptors for the  $X_2$  and O types.

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(1e—126)

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**The Adaptation of the Heist-Lacy Method for Determining the Bactericidal Activity of Whole Blood for Chemotherapeutic Investigations.**

*John A. Kolmer and Louis Borow, J. Infect. Dis., 31:116, Aug., 1922.*

The object of this investigation was to find a reliable technic for measuring the bactericidal activity of the whole blood, adaptable for use on a large scale in the course of chemotherapeutic studies with lower animals. The Heist-Lacy method was given an extensive trial.

The essential feature of this method is that a capillary glass tube is filled by capillary attraction up to a fixed mark with a broth culture of the medium, and then emptied. A certain number of bacteria remain sticking to the walls of the tube. Blood as it comes from capillary or vein is allowed to flow up the tube to the mark and the tube is then sealed and incubated. If the blood has no bactericidal action the bacterial which have remained on the wall of the tube find themselves in a favorable medium and multiply rapidly; if it is bactericidal they are killed and no growth results. Readings are made by blowing out the contents of the tube on a glass slide and staining and examining under the microscope. By combining several capillary tubes into one many-stemmed pipet and by using a series of ascending dilutions of broth and approximate quantitative value may be given to the test.

The authors' experiments were conducted by determining the bactericidal activity of the blood of normal rabbits before and at varying intervals after the administration of several compounds. Two microorganisms were used; a highly virulent Type I pneumococcus and a culture of *Staphylococcus aureus*. It was found that the Heist-Lacy method is a simple one to perform. If rabbits are employed, the test microorganism should be one capable of surviving and proliferating in the blood of these animals in order to elicit more clearly the possible bactericidal activity imparted by the drug under study. The administration of ethylhydrocuprein hydrochlorid to rabbits by intravenous, subcutaneous and oral routes results in rendering the whole blood decidedly pneumococidal. Similar, but much less marked results followed the administration of other quinin compounds as the bisulphate, hydrochlorid, and quinin and urea hydrochlorid. The bactericidal properties of the blood disappeared after the use of these compounds had ceased. It was found that large amounts of mercurophen raised the bactericidal activity of the blood of rabbits for pneumococci and especially for staphylococci. Mercuric chlorid caused a slight and irregular increase of the bactericidal activity of the blood of living rabbits for these organisms. This method has been found less susceptible to contamination and less laborious than plating methods for measuring the bactericidal activity of whole blood. Since only a few drops of blood are required it permits the use of small animals and repeated tests.

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**Hyperproteinemia Following Injections of Proteins. Experimental Contribution on the Pathology of Serum Protein and on the Question of Foreign Protein Therapy.**

*Wilhelm Berger, Ztschr. f. d. ges. exper. Med., Berlin, 28:1, June 7, 1922.*

Berger has undertaken determinations of the quantities of total protein, globulin and albumin in the serum of rabbits before and after repeated injections of human blood serum or sheep's red cells in suspension (5%), using Reiss's and Rohrer's technic. It became apparent at the outset that in normal, untreated animals the figures for the various protein constituents undergo only slight variations, the maximum oscillation not exceeding 0.8%.

The curve for total protein content following injections of sus-

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pensions of sheep's red cells seems to consist of 4 phases: (1) latency (lasting 24 hours); (2) initial decrease (lasting to the third day); (3) primary increase; (4) secondary increase. Between the third and fourth phases there is a distinct downward curve, the lowest point of which is reached as a rule between the thirtieth and the sixtieth day. The globulin curve consists usually of 3, occasionally of 4, phases: (1) latency (first to third day); (2) initial decrease, particularly noticeable following reinjection, which may amount to more than 50% of the normal globulin index; (3) increase, lasting at times from the fourth to the fiftieth day following injection, and amounting commonly to double the normal globulin content; the point of highest rise is reached ordinarily during the second week. Occasionally there is a fourth phase, of subnormal values. The albumin curve presents 3 phases: (1) latency, of longer duration than in the globulin curve; (2) decrease, also of longer duration, and of much greater intensity, than in the globulin curve; (3) increase, occurring only after the globulins have returned to normal, i. e. between the sixtieth and one hundred and twentieth days, and reaching to double the initial albumin index. A superimposition of the albumin and globulin curves will explain why the curve for total protein has 2 peaks; the first corresponds with the phase of globulin increase, the second with that of albumin increase.

Berger concludes that the protein content of blood serum varies not only according to changes in the water content of the blood, but also with the introduction or withdrawal of any of its constituents. The succession of events in such cases is invariably: (1) fibrin-globulin peak; (2) globulin peak; (3) albumin peak; it follows an elementary law of reaction in cellular pathology, according to which various pathologic phenomena occurring within a cell are made to depend on a transposition of the protein content toward the globulin side, which later manifests itself by changes in the body fluids. Hyperproteinemia does not seem to run parallel with the rate of precipitin production in the blood, and is probably dependent on an increased rate of tissue solubility. The facts observed should prove of clinical value, since they afford a good insight into the efficacy of foreign protein therapy; similarly, the technic employed is particularly suitable to the mass method of administration of such protein therapy.

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#### **Electrocardiographic Investigations of Anaphylactic Shock in Guinea-Pigs.**

*H. Königsfeld and E. Oppenheimer, Ztschr. f. d. ges. exper. Med., Berlin, 28:106, June 7, 1922.*

That pathologic manifestations on the part of the guinea-pig's heart—and probably also of blood-vessels—may and do occur in anaphylactic shock, has been reported in the experiments of Biedl and Kraus as well as in the works of H. Braun and of Auer and Lewis. However, all investigators whose reports have so far appeared leave unanswered the all-important question whether the visible disturbances in heart action, manifested under direct observation or actual blood pressure determinations in the form of fibrillation, incomplete contrac-

tions, and finally complete heart failure, are an immediate result due to absorption of anaphylactic toxins, whether they represent a primary anaphylactic reaction of the heart, or whether they arise secondarily through environmental influences or from changes due to asphyxia.

In the course of the authors' present experiments, guinea-pigs were rendered anaphylactic through injections and reinjections of 0.3-0.5 c.c. human blood serum. Heart contractions were registered by means of electrodes inserted into both poles of the viscus. A summary of the results obtained in 15 observations shows: In light anaphylactic attacks the heart action was unaffected. In serious anaphylactic conditions there occurred disturbances in conductivity, reaching gradually to complete dissociation, in the course of which the rate of the auricles was greater than that of the ventricles. During the stage of cardiac shock the *t*-wave was at times higher, at other times with the peak directed downward. The pulse rate fell rapidly and regularly with the onset of contractions, reaching one-half the normal rate within one or two minutes following the injection. Experiments with injections of ergotin previous to reinjection of serum showed that during immobilization and handling of the animal, i. e. during the entire preparatory stage of the experiment, there was no abnormal irritation of the sympathetic.

Electrocardiographic curves identically similar to those in anaphylactic shock are obtained in animals in the stage of asphyxia brought about by suppression of air intake. It is concluded from this fact that the heart disturbances observed during anaphylaxis may be accounted for as occurring in consequence of asphyxia.

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(1e—129)

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**The Physical Chemistry of the Alexin Fixation Reactions.**

*Julius Kiss, Biochem. Ztschr., Berlin, 129:487, May 23, 1922.*

The principles and methods of physical chemistry may be applied successively to the study of the alexin problem. Alexin is a distinctive substance consisting of hydrophilous colloidal particles which, however, cannot be divided without losing their characteristic properties. Alexin fixation follows the rules of physical adsorption. If a corresponding amount of kaolin be added to a serum containing alexin, the serum loses its activity. Bacteria are known to adsorb alexin. Measurements were carried out in such a manner that serum containing alexin was added to a known number of typhoid bacilli, and the alexin loss determined after a certain time. But the adsorption of alexin by typhoid bacilli results in its destruction. Agglutination of the bacilli is increased to a high degree in the presence of alexin, which likewise points to a similar relation of alexin to agglutinin. Therefore neither agglutinins, nor bactericidal immune bodies, nor other alexin-fixing substances exert any material influence on the nature of the process; they merely increase its intensity to a large degree. The results of investigations show that the various forms of alexin fixation, the nonspecific as well as the specific fixation reactions, take place in accordance with the regular rules of physical adsorption, and the adsorption formula is applicable to them. As the quantitative determinations in the titration of alexin are not very exact it may be properly maintained that the fluctuations are not excessively

great. This means that the character of alexin adsorption remains fairly constant in the most diverse reactions, whether simple or complicated. The hitherto current assumption, that the fixation of alexin is rendered possible only after the mutual anchoring of immune body and antigen, is conclusive only for blood-corpuscles. In general, however, antigens are to be regarded as adsorbents whose adsorbing capacity is increased in a particularly marked degree by specific reactions. These reactions are often attended by alterations of dispersity which are perceivable macroscopically. These dispersity alterations—floc-culation, precipitation, agglutination—contribute to the adsorption of alexin.

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**The Stability of Bacterial Suspensions. I. A Convenient Cell for Microscopic Cataphoresis Experiments.**

*John H. Northrop, J. Gen. Physiol., 4:629, July 20, 1922.*

Measurements of cataphoresis of particles in an electric field are complicated by the fact that in addition to the motion of the particles relative to the water, the water itself moves at the surface of the cell. Some of the cells devised by previous workers offset this and other difficulties somewhat. The author describes a very convenient cell which is made of a thin slide resting on strips of glass about 0.8 mm. thick cemented to a thick glass slide. Two blocks of thick glass are cemented on top of the cover-slide at each end of the cell. The ends of the cell are then ground smooth on an emery wheel. A piece of thick-walled glass tubing is widened and flattened at one end so as to cover the end opening of the cell. This flattened end is ground smooth and is cemented to the end of the cell. The same process is repeated at the other end of the cell. The best material for cementing the cell together the author found to be soft "De Khotinsky cement." The pieces of glass are warmed to about 80° in an air-bath, coated with a thin layer of cement and pressed together. For the calibration of the cell it is necessary to know the drop in potential per centimeter in the cell itself. Since the area of the connecting tubes, etc., in general, is different from that of the cell it is necessary to correct for this difference. If the apparatus as a whole is filled with the same solution, the total resistance of the solution will evidently be proportional to the length and inversely proportional to the cross-section. Since the drop in potential per centimeter is proportional to the resistance per centimeter, it is possible to calculate the drop in potential in the cell itself, provided the dimensions of the rest of the apparatus are known. In measuring the velocity of migration the cell is clamped in position under the microscope, after filling the electrode tubes with saturated zinc sulphate, and connecting the electrodes to a source of potential. The stop-cocks are turned so as to close the tubes containing the zinc sulphate and the cell filled with the suspension, care being taken to avoid air bubbles. The stop-cocks are then turned so as to connect them with the zinc sulphate solution, the circuit closed and the time required for a particle to cross a division of the micrometer eye-piece determined with a stop-watch. Owing to the migration of the water itself, it is necessary to obtain the average motion of the particles in the cell as a whole. This may be done accurately by determining the speed

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at various depths, say every 0.05 mm., plotting the curve so obtained and determining the mean height from the area as measured by a planimeter and the length of the base.

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**The Stability of Bacterial Suspensions. II. The Agglutination of the Bacillus of Rabbit Septicemia and of Bacillus Typhosus by Electrolytes.**

*John H. Northrop and Paul H. De Kruif, J. Gen. Physiol., 4:639, July 20, 1922.*

The authors made measurements of the potential and of the cohesive force at the surface of *Bacillus typhosus* and the bacillus of rabbit septicemia in solutions of various salts and acids. The potential was determined from the rate of migration described in the 2 preceding papers (in this magazine). The U-tube method was used for the experiments with the bacillus of rabbit septicemia and the microscopic method with *B. typhosus*. It was found that a comparative measure of the attractive forces between the organisms could be obtained by measuring the force required to tear apart 2 glass plates covered with a film of the bacteria and immersed in the solution which was under investigation. From these measurements, in conjunction with the measurements of the potential difference, it was found that whenever the potential difference between the surface of the bacteria and the solution was less than about 15 millivolts the bacteria agglutinated, provided the cohesive force was not affected. If the cohesive force is decreased, this critical potential is also decreased, and if the cohesive force is made very small, no agglutination occurs even though the potential be reduced to zero. It was also found that all electrolytes tested in concentrations less than 0.01 to 0.1 n. affect primarily the potential, while in concentrations greater than 0.1 n. the effect is principally on the cohesive force. In the case of bacteria sensitized with immune serum, the cohesive force remained constant and the agglutination could be predicted solely from the measurement of the potential.

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**The Stability of Bacterial Suspensions. III. Agglutination in the Presence of Proteins, Normal Serum and Immune Serum.**

*John H. Northrop and Paul H. De Kruif, J. Gen. Physiol., 4:655, July 20, 1922.*

Results of experiments on the effect of proteins and sera on the properties of suspensions of bacteria are given in tabulated and graphic form showing: (1) the effect of various concentrations of egg albumin on the agglutination and charge of the bacillus of rabbit septicemia (Type D strain); (2) the effect of the addition of globin to a suspension of Type D; (3) the effect of normal and immune serum on the pH curves of *Bacillus typhosus*. Tables show the effect of the pH on the amount of normal serum and immune serum to cause agglutination of

various organisms and the influence of NaCl concentration on agglutination with dialyzed normal and immune serum. From a study of these results one learns that the addition of proteins or serum to suspensions of bacteria, *B. typhosus* or rabbit septicemia, at different pH widens the acid agglutination zone and shifts the iso-electric point to that of the added substance. The amount of serum required to agglutinate is much less near the acid agglutination point of the organisms. The addition of immune serum prevents the salt from decreasing the cohesive force between the organisms, and agglutination therefore is determined solely by the potential, provided excess immune body is present. Whenever the potential is decreased below 15 millivolts the suspension agglutinates.

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**The Flocculation of Bacteria by Proteins.**

*Arnold H. Eggerth and Margaret Bellows, J. Gen. Physiol., 4: 669, July 20, 1922.*

In this investigation the effect of pure proteins on the stability of bacterial suspensions at different pH concentrations was studied. Several species of bacteria were used, but the most instructive results were obtained with a strain of *Bacterium coli* grown on beef extract peptone agar plates. The growth was suspended in 0.85% NaCl, filtered through paper, centrifuged, then centrifuged 3 times out of distilled water. In most of the experiments a temperature of 40° C. was maintained. Flocculation was observed macroscopically; no test was considered positive unless definite macroscopic flocks were formed, which settled leaving a clear supernatant fluid. The authors studied the flocculation of *Bacterium coli* with (a) gelatin, (b) egg albumin, (c) protalbumose and hetero-albumose, (d) edestin, (e) hemoglobin. A study of the tabulated results shows that the zone of flocculation of protein-treated bacteria bears a significant relationship to the iso-electric point of the protein used. With the higher concentration of protein, agglutination occurs at or near the iso-electric point of that protein; at reactions acid to this, the bacteria carry a positive charge and are not agglutinated. With diminishing concentration of protein, the zone of flocculation shifts toward and goes beyond that characteristic of the untreated bacteria. This was found to occur both in the presence and in the absence of salts.

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**A Serologic Study of the Gonococcus Group.**

*John C. Torrey and George T. Buckell, J. Immunol., 7:305, July, 1922.*

The primary purpose of this investigation was to determine whether gonococci may be distributed among a number of fixed immunologic types or whether, on the other hand, the strains exhibiting dissimilar serologic characteristics may more logically be considered as more or less labile variants from a common basal type. The authors' analysis by agglutinin absorption methods of the serologic relationships of 77 gono-



coccus strains, isolated from cases of acute and chronic gonorrhea and its complications, indicated that they may not be distributed among a number of clear-cut immunologic types. Although the investigation did not show the existence of distinct immunologic types to each of which a considerable number of gonococcus strains might be referred, it was found feasible to classify the strains under the 3 general headings of (1) regular, (2) intermediate and (3) irregular strains. Among the regular strains were found certain ones which were highly generalized from the antigenic standpoint, and which appeared to be representative of a large part of the gonococcus group. A marked degree of correspondence was noted between strain affinities as revealed by agglutinin absorption and complement fixation tests.

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**Serologic Examination of 100 Strains of the Gonococcus.**

*W. J. Tulloch, J. Path. & Bacteriol., Edinburgh, 25:346, July, 1922.*

The strains herein discussed were isolated from 100 cases of acute and subacute urethritis in the male of admitted venereal origin, and were so chosen as the sole source of the cultures in order to exclude the introduction into the series of the pseudogonococcus. The culture medium finally elaborated after much experimenting consisted of a mixture of trypsinized broth, trypanin, KCl, CaCl<sub>2</sub>, NaHCO<sub>3</sub>, and crystalline disodium hydrogen phosphate. To this was added a suitable quantity of agar and of extract of fresh ox heart, after preliminary boiling. On the media described, colonies of the gonococcus present these characteristics: They are usually discrete in primary cultures and after 48 hours' incubation at 37° C. are 1-3 mm. in diameter. They are slightly raised above the surface of the medium and appear to have a center area more elevated than the margins. The surface is glistening and the color pale gray, and when viewed by transmitted light the colonies are transparent. The most variable feature of the colony is the degree of transparency, the growths tending to be more opaque when cultivated on media that are more acid than pH 7.6 and more transparent on those which are more alkaline. The most constant feature of the growth is its peculiar mucus-like quality.

The authors' serologic investigation includes (1) a short review of recent literature, (2) preparation of suspensions of gonococcus for agglutination tests and for immunization of rabbits, (3) action of normal rabbit serum on suspensions of the gonococcus cultured and prepared as described, (4) technic of agglutination and absorption of agglutinins, and (5) results obtained on examination of 10 strains, taken at random, by the agglutination method, (6) specificity of agglutination as a means of identifying and classifying gonococci, (7) results obtained on applying the absorption of agglutinins test to the first series of 50 strains of gonococci isolated, (8) examination of Gordon's prevalent "type" strain, and (9) examination by the absorption of agglutinins test of a second series of 50 strains. From the resulting tabulated data the author concludes that 72% of cases of acute and subacute gonorrhea in the male are caused by one fairly clearly defined serologic type of the gonococcus.

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**The Serologic Relationships Between Strains of the Pfeiffer Bacillus. Influenza Studies. X.**

*E. O. Jordan and W. B. Sharp, J. Infect. Dis., 31:198, Aug., 1922.*

The majority of investigators have failed to find any antigenic relationship between strains of the Pfeiffer bacillus of epidemic origin. The possession of a large number of Pfeiffer bacillus strains isolated at different times and places gave a favorable opportunity to study the question. The method of obtaining an agglutinating serum was essentially similar to that followed by other observers. It was found that the particular strain of Pfeiffer bacillus used to produce an immune serum is usually agglutinated by the homologous serum more rapidly, more constantly and in higher dilution than any heterologous strain. Absorption tests throw little more light on the true biologic relationship of the different strains in this group than does direct agglutination. Usually each strain of Pfeiffer bacillus possesses a serologic individuality. Occasionally strains from different sources exhibit a serologic identity. As many as 3 serologic races may be present at the same time in the throat of one patient. There is no correlation between indol-producing powers and agglutinative affinities except possibly in strains isolated from meningitis. The lack of any definite serologic grouping among the strains of Pfeiffer bacilli is an indication that a distinct invasive type has not become fixed, and is an argument against regarding any member of this group as the primary causal agent in epidemic influenza. Possibly a race of "influenza meningitis" bacilli is in process of evolution.

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**Studies on Acute Respiratory Infections. XI. A Serologic Study of Alpha Streptococci from the Upper Respiratory Tract.**

*Agnes Goldman, J. Immunol., 7:361, July, 1922.*

Study of the relationship of alpha streptococci by means of direct agglutination and also absorption of agglutinins, was made for (1) detection of the presence or absence of groups which might indicate an epidemiologic relationship to influenza and other respiratory infections; (2) detection of possible correlations between colony, sugar fermentation and agglutination types; (3) comparison of strains from normal, cold and influenza cases; and (4) investigation of the more commonly encountered difficulties that limit the value of tests for the differentiation of the particular type of organisms studied. Work was done on strains, from 33 cases, taken from 16 influenza patients, 2 doubtful influenza patients, 6 cold cases, 6 normal individuals, 2 measles cases and an influenza case. Altogether, the author reports on 112 strains isolated from the above sources. The serums studied were obtained by immunizing rabbits against each of 7 strains.

The tabulated results show that direct cross-agglutination, even with strains of the same case, is not necessarily a proof of complete identity. Cross-agglutinating strains from other cases absorb agglutinins in different amounts. The absorption tests with serums produced by several strains of the same case lead the author to conclude that she was not dealing with absolutely fixed type organisms.

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**The Precipitin Test in the Detection of Bacterium Diphtheriae.**

*G. H. Smith and C. E. Kaufman, J. Lab. & Clin. Med., 7:619, July, 1922.*

An attempt has been made to adapt the precipitin test to the detection of Bacterium diphtheriae. By this method it seemed possible to shorten the period necessary for making a diagnosis. Furthermore, with a specific serologic test the differentiation between B. diphtheriae and pseudodiphtheria forms could be made less difficult. The precipitating serums were derived from 2 sources, (1) rabbits immunized with single, freshly isolated, virulent strains of B. diphtheriae and (2) anti-diphtheritic horse serum. In addition, control immune serums were produced with diphtheroid organisms.

For preparing the antigen, extracts of B. diphtheriae were secured by breaking down the organism with an alkali hypochlorite solution. By this method satisfactory antigen can be derived from nose and throat swabs taken directly from the patient. By eliminating cultural procedure a saving of at least 12 hours is obtained. The method of extracting the antigen is essentially that of Krumwiede and Noble.

The test itself consists in layering these extracts upon the precipitating serums. In order to conserve serums and to conduct the reaction with minimal amounts of concentrated antigen the tests are set up in small tubes of about 4 mm. diameter. As a rule the reaction appears almost immediately in the form of a ring of precipitate at the point of contact of the 2 liquids. The reactions are always controlled by combination of the antigen with a normal serum and with a diphtheroid immune serum. When B. diphtheriae was present on the swab in sufficient numbers to yield a positive culture the precipitin test was positive in 97.7% of the cases. With specimens culturally negative the precipitin test agreed in 73.4% and the discrepancy between the 2 methods is in the direction of an excess of positive findings with the serologic method. This suggests that organisms may be detected by the serologic method even though they are present in numbers insufficient to give a positive growth upon media when inoculated in mixed culture.

The greatest possibilities for error in performing the test are associated with a too great acidity or alkalinity of the precipitinogen, or in failing to drive off all alcohol during the final heating. In no instance were there observed any nonspecific effects due to the presence of other organisms in association with B. diphtheriae upon the swabs.

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**Refractometric Researches on the Reactions between Isolated Cancer Cells and Blood-Serum. II.**

*Robert Koritschoner, Biochem. Ztschr., Berlin, 129:605, May 23, 1922.*

In relation to a series of refractometric investigations communicated regarding the reactions between isolated cancer cells and blood-serum (Freund-Kaminer reaction), the question is whether the decomposing substance in carcinoma-serum in Abderhalden's and Pregel's methods is identical with the destructive substance in normal serum

(Freund, Kaminer, Neuberg and Koritschoner, Morgenstern) and is conditioned merely by the difference in the material.

Results show: In 20 out of 22 investigated serums of afebrile, carcinoma-free individuals the reaction with prepared carcinoma cells increased the serum's refractive power; in 20 serums of afebrile, carcinoma patients and in 7 out of 8 serums of carcinoma-free, febrile patients it was diminished. In 13 out of 22 serums of carcinoma-free, febrile patients the reaction in serum heated to 60° C. was reversed, as also in 14 out of 20 serums of afebrile, carcinoma patients. In 7 out of 8 serums of carcinoma-free, afebrile patients the reaction was reversed by addition of 2% sodium thiocyanate to the serum and likewise in 11 out of 20 serums of afebrile, carcinoma patients. In 7 out of 8 serums of carcinoma-free, febrile patients the refractive power was unaltered. Where there were simultaneous inactivation and addition of sodium thiocyanate to the serum, both before and after inactivation, reversal sometimes took place and was sometimes absent. In 5 out of 6 serums of carcinoma-free, afebrile individuals the reaction was reversed on allowing the serum to stand on ice 14 days; in 4 out of 6 serums of afebrile, carcinoma patients likewise; in 4 serums of carcinoma-free, febrile patients no reversal took place. On activating or adding sodium thiocyanate to these serums kept on ice during 14 days, a reversal of the reaction again took place in most cases.

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#### **Biologic Activators.**

*K. Kottmann, Schweiz. med. Wchnschr., Basel, 52:695, July 13, 1922.*

In principle the author's photoserologic method consists in generating colloidal silver salts in the serum. The serum is then exposed to light and hydrochinon is added, whereupon the serum assumes a brown tint. The time required to develop the reaction furnishes a standard for the distribution of the silver, and for that of the serum colloids.

From several protocols it appears that the photoserologic reaction is delayed by normal organs, but especially by organs with carcinomatous changes. A similar delay was experimentally proved for plant tissues. Alcoholic extract of cod-liver oil, or cod-liver oil with the addition of serum, acted in the same manner. Similar results were obtained in experiments with wine and grapes. All these observations seem to indicate that analogous serologic results are due to reaction bodies which in part are thermolabile, in part thermostabile, and which evidently are effective in minimal amounts, apparently in the manner of chemical activators. The same thing has been found for vitamins. To the endogenous organic vitamins, or the endogenous activators which occur in specially active form in carcinomatous tissue, the author opposes the active principle of turnips, cabbage, milk, bran, etc., which he calls exogenous activators. These are further divided into those influencing growth and other specific nutrition varieties. There follow tests of the reaction with the serum from various pathologic conditions and an extract of turnips. The characteristic inhibition of the action of turnip bodies in carcinomatous serum suggests antitrypsins. Possibly there is involved the presence of antigrowth substances by

means of which the organism reacts to the lawless and boundless growth of the tumor. Relations to some of the consequences of cancerous disease, e.g. cachexia, must also be considered.

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**Researches on Precipitation Types.**

*Friedberger and Meissner, Klin. Wchnschr., Berlin, 1:1248, June 17, 1922.*

Precipitins exhibit the remarkable fact that a definite protein forms precipitins in the rabbit, not only against itself (specific or isogenetic) and against the protein of related animal species (homeogenetic), but also against that of distant species (heterogenetic). In rabbits treated 3 or 4 times with 1 c.c. antiserum intravenously, such strong serums reacting against heterologous protein occurred in 15% of the animals previously treated with the most diverse antigens. If, in certain antisera, Konew's test with the homologous protein and with a heterogenetic one be compared, no difference is usually observed by incident light, while by transmitted light the specific precipitates are cloudier than the heterogenetic ones. Examination with the agglutinoscope and microscope shows that the specific (isogenetic) protein is precipitated by precipitating serums in large loose flakes, the heterogenetic protein in dense flakes. The homeogenetic reaction is a transition between both types but dense flocculation predominates. The complement deviation in these serums was found to be specific with reacting serums in contradistinction to precipitation. This indicates that the specific loose precipitates are the carriers of the complement deviation reaction, conversely to the behavior of complement deviation in PX 19 bacteria and bacteria of the typhoid group. On precipitating heterogenetic reacting serums with heterogenetic unwashed blood-corpuscles the heterogenetic precipitin was lost, while the isogenetic was almost entirely preserved; it had become strictly specific. If, on the other hand, precipitation is effected by means of isogenetic unwashed blood the specific and non-specific precipitins are precipitated. This would seem to show that the reacting antigen contains receptors corresponding only to the dense, whereas the homologous antigen contains receptors corresponding to loose and dense precipitins, so that, contrary to homologous protein, not only loose but also dense precipitins should be present, which is confirmed by microscopic examination. The protein of related animal species behaves in the precipitation test more like the isogenetic. By precipitation with boiled albumin only the heterogenetic thermolabile precipitin is abstracted.

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**General Considerations of the Sodium Chlorid Concentration in Serologic Reactions.**

*Robert Brand, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34:304, June 28, 1922.*

From a review of the literature on the significance of sodium chlorid concentrations for the Meinicke (third modification), the Sachs-Georgi and the colloidal gold reactions, and from a series of experiments in which the serum employed was progressively diluted in such



a way that the addition of a 2% salt solution caused the maximum precipitation of undiluted serum, and higher concentrations of sodium chlorid solution produced equally great precipitation (due to the greater dilution of the serum), the author concludes that serums differ from one another only with respect to precipitation, protective serums being all identical. Further experiments with the flocculation reaction on positive serums, as well as on mixed serums containing a small amount of negative serum, to both of which were added sodium chlorid solutions in increasing concentration (resulting in a greater degree of precipitation with the higher dilutions) confirmed this postulate; there was also substantiation of the fact that both the protective and precipitation properties of the serum are enhanced by the addition of concentrated sodium chlorid solution. It was evident that the high sodium chlorid concentration affected only the serum, and not the extract. It thus depends entirely on laboratory technic, whether the end-result of a serologic test is facilitated or actually impeded.

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**The Properties of Syphilitic Sera in Relation to the Specificity of Immunity Reactions.**

*J. Holker, J. Path. & Bacteriol., Edinburgh, 25:281, July, 1922.*

The changed conditions of serum occurring in disease have been accounted for by 2 main theories, that of Ehrlich, and that of Bordet. The former is unsatisfactory because of the complicated terminology. Bordet's view depends on the purely physical theory of adsorption of Gibbs. A new theory of adsorption has arisen which Holker believes will be of great value in the study of immunity. Adsorption depends in general upon the nature, the arrangement and the spacing of the atoms forming the surface layer of the colloid. Applying this theory to serum, the "checker-board" of the serum colloid is changed during disease, and it is the infinite number of possibilities in the way of arranging the surface of a crystallocolloid complex which is responsible for the marked specificity of serum reactions. Serum is a colloid of the emulsoid type. An emulsoid colloid is one in which the 2 phases are both liquids, in contradistinction to a suspensoid colloid, in which the dispersed phase is a solid and the medium a liquid. Properties which distinguish an emulsoid from a suspensoid are its marked viscosity, stability to electrolytic salts, and protective power in preventing the precipitation of other colloids.

Previous observers have noted the increased viscosity of syphilitic serum, which is due to the increased amount of euglobulin which it contains. Granted that there are a greater number of large particles in serum during disease, as is evident by the increased amount of euglobulin and pseudoglobulin, it follows that the protective power of such serum must be materially used up in preventing such particles from precipitating. It occurred to the author therefore that it might be useful to compare the protective powers of syphilitic and of normal serum in preventing the precipitation of a suspensoid colloid by an electrolyte. A stable suspensoid was obtained by rapidly diluting with distilled water an alcoholic extract of guinea-pig's heart to which was added an alcoholic solution of cholesterin. The suspensoid so obtained showed

a faint bluish opacity. On adding physiologically normal saline to the suspension in distilled water, the antigen, however, rapidly precipitated. Measurement of the protective power of the serum involved a measurement of the opacity of the antigen in distilled water, in saline, in the presence of normal and of pathologic serum. This was accomplished by the use of a special apparatus previously described by the author. The reagents were all made up in distilled water and the respective tubes contained: (1) positive serum plus antigen; (2) negative serum plus antigen; (3) positive serum alone in distilled water; (4) negative serum alone in distilled water; (5) antigen alone in distilled water. The turbidities were measured at intervals, and were later plotted against the times. The curves show that both positive and negative serums have affinity for the so-called antigen, and that the difference between a positive and a negative serum is quantitative rather than qualitative. The control curves provide further evidence that the euglobulin is increased in syphilitic serum.

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**The Opacity of a Mixture of Serum and Wassermann "Antigen" in Progressively Increasing Concentrations of Sodium Chlorid.**

*J. Holker, J. Path. & Bacteriol., Edinburgh, 25:291, July, 1922.*

Holker has previously shown that the results obtained on mixing serum and Wassermann antigen differ widely according to whether physiologically normal saline or distilled water is used in diluting the antigen. It was found that only in the presence of the saline were the results suggestive of the changes occurring in the Wassermann reaction. Physiologically normal saline thus was not merely an inert substance used for maintaining the correct osmotic pressure for the red corpuscles, but was closely associated with the specificity of the Wassermann reaction. It was deemed advisable, therefore, to extend the investigation and to test the effect of progressively increasing concentrations of sodium chlorid on the complex. The method of following the changes which took place was to measure the opacity of the complex suspension by means of an opacimeter. Although 3 different methods were used in mixing the serum and antigen, in all methods the final concentration of serum and antigen was the same, i. e. the serum was diluted 5 times and antigen was diluted 50 times. The results obtained are shown graphically, the opacity of the suspension being plotted against the concentration of the added saline. The results of all 3 methods indicate that the protective power of syphilitic serum is less than that of normal serum.

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**Standardization and Preservation of Complement Serum for Wassermann Test.**

*E. H. Ruediger, J. A. M. A., 79:551, Aug. 12, 1922.*

About 2 years ago the author showed that a number of complement serums from guinea-pigs gave results with the same human serum varying from 2+ to 10+. Even greater differences have been observed since; serums from some guinea-pigs have given negative

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results while serums from other guinea-pigs gave 10 + with the same human serum. The serums from different guinea-pigs differ greatly in fixability and in hemolytic power. In order to obtain fairly uniform complement serums, they must be selected, only the good ones being used. Breeding only guinea-pigs with good complement for 3 years greatly improved Ruediger's collection of guinea-pigs for this purpose. Any raw vegetables such as potatoes, cabbage or carrots, prevent scurvy and are suitable winter feed for complement guinea-pigs. A mixture of raw vegetables gives the best results. The fixability of guinea-pig complement was much better in winter than in summer, which may be due to the large quantity of grass fed in summer. Among the methods commonly employed to preserve complement serum, freezing the serum or salting the serum appear to be the most successful. Frozen complement serum kept below 0° F. in the cold storage room remained active for 8 weeks. Salted complement serum kept at approximately 1° C. remained active for more than 4 weeks.

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**Nonspecific Complement Fixation in Wassermann Reactions.**

*W. Bachmann, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34:319, June 28, 1922.*

The Wassermann reaction is very often positive in rabbits, without any plausible reason. The author thinks that variations in the reaction, similar to those obtained with rabbit blood, may also occur with human blood, and assumes for this purpose that the "reaction bodies" which render complement fixation possible are products of decomposition of white blood-cells. The probability of the correctness of this assumption must not be underestimated, particularly in view of the fact that in scarlet fever, simultaneously with a nonspecific positive Wassermann, there is eosinophilia, and of the various nonspecific positive Wassermans obtained in the course of other acute or chronic intoxications, each of which is accompanied by some change in the blood picture. Jacobsthal and Pappenheim suspected that decomposition of leukocytes leads to the production of complement-fixation bodies; the latter believed that the fragments of white blood-cells are not the only source of reaction bodies. Wassermann himself pointed out that the positive complement-fixation reactions obtained with cerebrospinal fluids of paretics are attributable to substances elaborated by or derived from the lymphocytes in the spinal fluid. Wassermann arrived at this conclusion after experimental demonstration that the products of autolysis of such lymphocytes increased the intensity of positive reactions, while the same products of autolysis, when added to the cerebrospinal fluid of nonsyphilitic individuals, failed to produce a similar increase in reaction intensity.

Bachmann maintains that there is no interrelation between the leukocyte count in the blood and the Wassermann reaction; on the other hand, pseudo-eosinophil count variations seem to exert some influence on the reaction. The Dold opacity reaction and the syphilitic flocculation test (Sachs-Georgi) are negative even with rabbits' serums which react positively to the ordinary Wassermann test. The positive serum of rabbits displays different properties from those of positive

human serum in the sense that the whole serum reacts more strongly positively than the globulin fraction, whereas the albumin fraction may even yield a frankly negative reaction. Intravenous introduction of cholesterin into the rabbit does not exert the same influence on the Wassermann reaction that the addition of this substance causes in man.

Various changes to which the serum had been subjected (exposure to bacterial action, mixture with sheep's blood-cells, with animal charcoal and kaolin) failed to influence the outcome of the Wassermann reaction in the least. On the other hand the addition of a minute amount of chloral hydrate (0.1-0.2 c.c. 10% solution) to a negative serum promptly converted the latter into a positive one, whereas the addition of 0.5 c.c. 15% solution of chloral hydrate to a positive serum transformed the latter into a negative one. These changes in the reaction are probably caused by the addition of acid or alkaline material.

Bachmann has observed (after the addition of solutions of chloral hydrate of given concentrations to either positive or negative serums) that there occurred definite flocculation in the latter. It is quite possible that this phenomenon has a special significance.

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**The Inhibitory Effect of Saponin on the Syphilis Flocculation Reactions (Sachs-Georgi and Meinicke Reactions); Also on the Sachs-Guth Flocculation Reaction for the Demonstration of Heterogenetic Antibodies, in Contrast to the Negative Effect of Saponin on the Precipitation Reaction of Uhlenhuth.**

*P. Niederhoff, Münch. med. Wchnschr., 69:929, June 23, 1922.*

The author upholds the view that, in the first place, electric forces are probably not responsible for the formation of flocculi in the positive reaction for syphilis, but that the principle of the absorption and discharge of water (swelling and dehydration) deserves consideration in the understanding of the formation of flocculi. Accordingly, the formation of flocculi would first of all result from a dehydration of the extract lipoids under the influence of the syphilitic changes in the serum. On investigating these questions, saponin was found to have an inhibitory action on the course of the syphilis flocculation reaction: It prevents the formation of flocculi in a positive Sachs-Georgi reaction; weakens to a greater or less extent the formation of flocculi in a positive Meinicke reaction; almost completely destroys the flocculation reaction for the demonstration of heterogenetic antibodies of Sachs-Guth, in its positive course; but does not seem to affect the Uhlenhuth precipitation. The point of attack of the saponin effect in the flocculation reactions of Sachs-Georgi, Meinicke and Sachs-Guth probably lies in the extract lipoids.

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**Studies of Cerebrospinal Fluid and Blood of Syphilitic and Normal Persons, with Special Reference to the Immunity Reactions and the Colloidal Gold Test on the Original and Ultra-filtered Fluids and Serums.**

*Charles E. Nixon and Koichi Naito, Arch. Int. Med., 30:182, Aug., 1922.*

The globulin fraction in syphilitic serum contained the active substance in the Wassermann reaction. The filtrability of globulin in

syphilitic serum by the ultrafilter was less than that in the normal serum. Three factors have been considered in this relationship: (1) the possible ease of adsorption of the Wassermann reaction active globulin of the ultrafilter as compared with normal globulin; (2) the possible greater size of the particle of active globulin as compared with normal globulin, and (3) the possible instability of the active globulin as compared with normal globulin. Positive colloidal gold reactions were due to the presence of precipitating substances. Both precipitating and protecting substances were present in pathologic cerebrospinal fluid. Curves in Zones 1, 2 and 3 were due to varying amounts and proportions of the precipitating and protecting substances. Albumin and globulin may possess both precipitating and protecting power. Ultrafiltrates of syphilitic and nonsyphilitic serums gave curves that were more or less similar, but there tended to be a greater difference between the zones of reduction of the original and filtered serum in syphilitic than in normal cases. The protecting substance was decreased by ultrafiltration to a greater degree than the precipitating substance. Changes in the state of the protein modified precipitating and protecting powers. The salt solution test in the colloidal gold test partially neutralized the protective action.

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**A New Syphilis Serum Reaction with Perethynol Obtained by Means of the Serum of Guinea-Pigs Injected with Sheeps' Red Cells.**

*Hector Diacono, Arch. d. Inst. Pasteur de l'Afrique du Nord, Tunis, 2:219, No. 2, 1922.*

Perethynol is an extract prepared by exhausting the equine heart in ethylene perchlorid and absolute alcohol. It is remarkably constant and yields 15 gm. dry extract per liter. Flocculation produced by a serum when added to perethynol is standardized by a hemolytic system consisting of guinea-pig serum and sheeps' red cells. Vernes has described the general principles of the process. The author has devised a sure and standard diagnostic method. The reagents required are sheeps' red cells, a fine suspension of perethynol and the serum of guinea-pigs containing antibodies formed following injection with sheeps' red cells. NaCl solution (9:1000) receives the sheeps' red cells. The suspension should be such that, on adding 0.8 c.c. of it to 1.8 c.c. distilled water to make a total of 2.6 c.c., the mixture produces a color corresponding to No. 8 of the Vernes color scale, when placed in a hemolysis tube 13 mm. in diameter. For the perethynol suspension, a 25% dilution in normal saline is first prepared by agitation with a mechanical screw making 200 turns per minute. The perethynol is poured into the saline. When the suspension is thus obtained, it is made up to 1:40 by adding 9:1000 NaCl solution.

The antiserum is obtained by making, in guinea-pigs, every 2 days, 5 or 6 injections, each of 1 c.c. well washed sheeps' red cells. A very active antiserum is thus produced. A constant supply may be had by injecting a number of animals, which should be male. The animal is bled while it is fasting, the blood defibrinated and the serum, collected by the centrifuge, made up to a 1:10 dilution with normal saline. For



titrating, 4 c.c. of the 1:10 dilution of the antiserum are placed in a suitable vessel. In each of 12 hemolysis tubes, 13 by 60 mm., 0.2 c.c. of human healthy serum, warmed to 55° C., are placed. By means of a syringe graduated in 0.4 c.c., 0.4 c.c. of the 1:10 serum dilution are placed in the first tube, and 0.4 c.c. normal saline are substituted for the serum thus withdrawn from the vessel, whose contents are well mixed, but without foaming, by means of the needle of the syringe; 0.4 c.c. of the new dilution are placed in tube 2; 0.4 c.c. saline are again added to the vessel supply; tube 3 is prepared and so on until all the tubes are ready. They thus contain quantities of guinea-pig serum diminishing from 0.04 c.c. to 0.013 c.c.

In each tube are placed 1.2 c.c. perethynol suspension of 1:40. The tubes are incubated for 1 hour at 37° C. and 0.8 c.c. of the sheeps' red cell suspension are added. The results are read after a second similar incubation for 30 minutes. By centrifugating all the tubes, the hemolytic power of the different quantities of guinea-pig serum are shown. The quantity required for the syphilis reaction is the smallest quantity producing total hemolysis. It corresponds to No. 8 of the color scale, with practically no sediment of red cells. The quantity ranges from 0.036 to 0.018 c.c. guinea-pig serum. For the syphilis reaction, the serum examined is heated at 55° C. for 30 minutes and 0.2 c.c. are placed in each of 2 hemolysis tubes 13 by 60 mm. Tube 1 receives 1.2 c.c. 1:40 perethynol suspension. Tube 2 receives 1.2 c.c. normal saline. The guinea-pig serum, in quantity as determined above, is made up to 0.4 c.c. with normal saline and thus added to each of tubes 1 and 2. The latter are incubated for an hour at 37° C., 0.8 c.c. sheeps' red cell suspension are added, and the tubes again incubated, the progress of hemolysis in the check tube being noted. It is usually complete in 15-30 minutes. The perethynol tube is then centrifugated and the result read by comparison with the color scale.

This method is superior to Vernes' because excess albumin is avoided. The quantities of guinea-pig serum employed are 8-10 times less than the amount of guinea-pig serum required in Vernes' reaction. The method is much more simple than the Wassermann. Its greatest advantage consists of the hemolytic system used. The latter is perfectly equilibrated because the laws of supply and proportion governing the relations of alexin and sensitizer in the hemolytic complex are observed naturally, and without calculated corrections.

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### **The Influence of Anesthesia on the Restoration of the Volume of the Blood After Hemorrhage and After Transfusion.**

*A. E. Boycott and C. Price Jones, J. Path. & Bacteriol., Edinburgh, 25:335, July, 1922.*

The authors' experiments for the comparison between anesthetized and nonanesthetized animals were made on rabbits in which the duration of the bleeding was between 4 and 5 minutes and the quantity of blood removed about 40% of the total. The blood volume was then determined and the results recorded graphically. In the nonanesthetized animals restoration of volume began at once and continued steadily until complete in about 3 hours. In the rabbits under ether and urethan the

intake of fluid from the tissues during the bleeding and 4½ hours afterwards is about as quick but afterwards slows or stops altogether, and the volume remains without any substantial alteration for several hours. This slower and less complete restoration of blood volume after hemorrhage in anesthetized animals, is attributed to a diminution in the permeability of the capillary wall to liquid passing from the tissue fluid to the blood.

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**Hematophagy and Hemetaboly as a Normal Function of Various Types of Tissue-Cell (*Continued*).**

*H. M. Woodcock, J. Roy. Army M. Corps, London, 39:14, July, 1922.*

Following the exposition of his views of the mode of formation of the colloid of the thyroid gland, Woodcock adds certain negative observations, pointing in the same direction. The epithelial cells of the follicle do not contain iron, apart from the chromatin in their nuclei, hence the colloid can obtain the quantity of iron which is invariably present only from the hemoglobin of the red corpuscles. He fails to find the slightest evidence of the origin of the colloid in and from the protoplasm of the cells themselves and he has searched the literature in vain for anything that could be taken as an indication of such. Neither can he find any indication of the reabsorption of the colloid by the cells.

He thinks that in addition to the colloid there may also be present, in the lumen of the follicle, some liquid substance which has been created by and in the epithelial cells themselves; a true secretion which is the result of hemetaboly. The production of this secretion stands in close relation with the question of the characteristic crenations often shown by the colloid, which are regarded by many as due to shrinkage or retraction, but which Woodcock thinks represent different conditions occurring in the follicle during the course of the true secretory process. He thinks these clear, apparently empty areas, were occupied in life by a true liquid secretion of the cells, and that during the preparation of the sections, this liquid has, in all probability, been washed away. There is not the slightest evidence of the transformation of the secretion into colloid. Woodcock has only seen this secretion taking place into a lumen already containing formed colloid and never has he seen any indication of actively secreting cells in the case of an empty follicle. It seems possible that the secretion may dissolve a certain amount of the colloid, and then leaves the lumen of the follicle and is conveyed to the body in solution. It appears as if the functional activity of the growth in colloid formation were concentrated on the production of colloid material only, by means of hemetaboly.

Further, the exercise of this function of hemetaboly is not normally restricted to the macrophages, and it may be assumed that tissue cells of many types are accustomed normally to the exercise of this function for particular purposes, being able, by means of specific ferments, to form either largely or entirely, from hemoglobin, manifold and widely different substances (coming in the category of secretions and excretions). Furthermore, at times, certain "weakly" individual tissue cells, capable of exercising a hemetabolic function, pass into a condition of

physiologic depression or exhaustion, in which cell equilibrium is disturbed. Finally, as a biologic response to reaction—in a strenuous endeavor to recuperate their vitality—such individual cells become able to assimilate rich nutriment largely or entirely for their own use, as if they reverted somatically to the state of single-celled animals; and not content merely with red corpuscles, they take to ingesting and digesting leukocytes and other cells, containing chromatin, with its complex neucloproteins. Remembering, for comparison, the giant cell characters of megakaryocytes, what would be in all probability the inevitable outcome of this abnormal mode of behavior and alteration in cell metabolism? Would it not have a bearing on the origin of malignancy?

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**A Study of the Effect of Electrolytes on Hemolysis.**

*Hedley D. Wright and Peter MacCallum, J. Path. and Bacteriol., Edinburgh, 25:316, July, 1922.*

This investigation of the action of various salts in relation to hemolysis arose out of some observations made on the so-called zone phenomenon, in relation to bacteriolysis. In the investigation the hemolytic system used was: sheep cells, Burroughs Wellcome and Co.'s hemolytic serum for sheep cells, and guinea-pig serum as complement. The batch of hemolytic serum was the same throughout. The dilutions of complement and hemolytic serum were made in 0.85% NaCl solution. Eight rows, each containing 8 tubes, were arranged, and into each tube were put equal volumes (0.2 c.c.) of the appropriate dilution of each ingredient. These were well mixed and then, from a graduated dropping pipet, one drop of a suspension of sheep cells in a dilution of 1:6 was added. The tubes were then incubated for ½ hour at 37° C., and allowed to stand in the ice-box till next morning, when readings were made. The phenomenon was constantly observed, but it did not always appear at a constant concentration of the hemolytic serum.

To see if the rôle of the so-called inert substances, present in the serum in the form of its colloidal constituents, could be determined, an experiment was carried out at the same time as the above, and with the same materials, in which the dilutions of hemolytic serum and complement were made in inactivated normal human serum instead of physiologic saline. A control showed that the human serum was only very slightly hemolytic, 0.2 c.c. giving only slight hemolysis with complement diluted 1:10 in physiologic saline. In studying the inhibitory effect of electrolytes on hemolysis by hemolytic serum in physiologic saline mixtures, the experiments were arranged in such a way that the ultimate mixture always contained 0.85% NaCl. The inhibitory effect of the different salts was estimated by adding various amounts of an appropriate solution of the salt and making up to constant volume by means of distilled water. This was accomplished by putting in 12 successive tubes increasing amounts (0.1-1.2 c.c.) of the solution of the electrolyte to be tested. Sufficient distilled water was then added to each tube to bring the total bulk to constant volume of 1.2 c.c. Then 0.2 c.c. of complement diluted in 3.4% NaCl (equals 4 times isotonic concentration), and 0.2-c.c. of a 2% suspension of sensitized sheep cells in NaCl of the same concentration, were added to each tube. The resultant

mixture was therefore of a total volume of 1.6 c.c. The NaCl was throughout of a constant concentration of 0.85%. The contents of the tubes differed from one another in the concentration of the salt to be tested and consequently in the tonicity of the mixture. The influence of this latter factor was estimated simultaneously by the use of a non-electrolyte (glucose) in varying concentrations. By observing the tube in which, under the conditions of the experiment, hemolysis ceased to be complete, it was possible to determine the amount of an electrolyte required to effect this inhibition. The degree of sensitization employed was the equivalent of 5 M.H.D.

The tabulated results show that the power of various salts to inhibit hemolysis in saline menstrooms appears to be related to the valency of the ions present, both anions and kations. It was also observed that combination of complement with sensitized cells is prevented in isotonic glucose solutions. This inhibition of hemolysis can be overcome by different electrolytes in varying degrees. Power to restore hemolysis in glucose has an inverse relationship to power to inhibit hemolysis in physiologic saline.

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**Experimental Investigation of Intravital Hemolysis. III. Mechanism of Segregation of Heterogeneous and Toxic Auto-genous Blood Cells.**

*R. Bieling and S. Isaac, Ztschr. f. d. ges. exper. Med., Berlin, 27:154, June 7, 1922.*

This part of the work covers experiments on white mice, who received 0.5 c.c. washed sheep's red cells by intravenous injection; the animals were then bled at various intervals, and the blood of each animal collected in physiologic sodium chlorid solution containing sodium citrate. The blood and citrate mixture was centrifuged and the supernatant fluid decanted off; the spleens were macerated and filtered, the filtrate being separated off; both sediments were placed in sodium chlorid solutions. The spleen filtrates were red, and by appropriate dilutions could be made to approach a standard solution for purposes of comparison. Both blood and spleen sediments were mixed either with complement alone or with both complement and hemolysin, and the degree of hemolysis observed and marked down. The following results were obtained: The blood sediment was shown to contain sheep's red cells partly saturated with amboceptor and partly not; in no case was hemolysin found in them. The spleen was shown to contain the greater number of heterogeneous red cells, all saturated with amboceptor. Hence enlargement of the spleen and brown-red coloration of this organ in such experiments. The spleen also contained free hemoglobin (hence the red color of spleen filtrate), and the residue consisted overwhelmingly of sheep's red blood-cells.

From these findings the authors conclude that sheep's red blood-cells introduced intravenously acquire, while in circulation, hemolysin to the point of saturation, and are then caught by the spleen and retained there. Experiments with other organs showed that in the liver, for instance, there occurs only slight hemolysis, whereas in the kidneys no

hemolysis at all takes place. Similar experiments on the organs of white mice yielded identical results, except that, on the whole, hemolysis was less pronounced in these animals, since there was found a smaller quantity of normal hemolysin available for sheep's red cells, and there was formed a correspondingly smaller amount of immune hemolysins. In the rabbit, 20 minutes after injection one can recover the heterogeneous red cells fully saturated with amboceptor. However, these disappear rather rapidly from the circulation, being retained in the spleen. Similar experiments were carried out on mice which, instead of heterogeneous red cells, received injections of phenylhydrazin (6 injections, each containing 0.5 gm. phenylhydrazin in 1:5000 solution). The results showed disappearance from the circulation of the poisoned red cells, which were later found retained in the brown-colored, swollen spleen. There was hemolysis here, without any demonstrable free or combined amboceptors. The spleen was also found to contain free deposits of the poisonous substance. Spleen filtrate obtained from such animals colored red cells brown. No reactions of similar intensity could be obtained with the solid sediment of other organs (liver, kidneys) or of the blood.

Experiments on a horse which had received injections of red cells of other horses, showed that even erythrocytes which become saturated with isohemolysins are finally segregated in the spleen. All experiments therefore point to the fact that the spleen possesses the property of removing from the circulating blood all red cells affected by either immune serum or some poison, and all heterogeneous red blood-cells, retaining them within itself, and finally dissolving them.

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#### **Experimental Investigation of Intravital Hemolysis. IV. Rôle of Capillary Endothelium.**

*R. Bieling and S. Isaac, Ztschr. f. d. ges. exper. Med., Berlin, 27:180, June 7, 1922.*

The technic for these experiments was the same as the one described in the previous article; experiments were conducted only on mice, whose previous preparation included either extirpation of the spleen, blocking of the capillary apparatus by injections of saccharated ferric oxid (0.1 gm. in 0.3 sodium chlorid), or both these procedures combined.

Animals who had first received the saccharated ferric oxid solution and who were subsequently injected with sheep's blood showed neither swelling of the spleen nor increase in hemolysis in this organ through enhanced activity of normal hemolysins. To explain this, one may assume some disturbance in the production of either complement or hemolysin. Similar experiments on splenectomized animals showed no disturbance in complement production, since the intravenous introduction of immune hemolysin resulted in intravital hemolysis and icterus. Guinea-pigs were injected with such tremendous quantities of saccharated ferric oxid that they displayed grave symptoms of intoxication; yet there was no change whatever in the complement content of their serum. From a similar line of reasoning the saccharated ferric oxid



cannot be regarded as exerting any deleterious effects on prepared hemolysin.

However, the authors were able to demonstrate experimentally that splenectomized mice, after receiving such injections, reacted to single immunizing sensitization tests by the production of most minute amounts of hemolysin, indeed at times producing no hemolysin at all. Splenectomy alone, or the injections alone, with resulting capillary blocking, did not in the least affect the action of hemolysin. Simultaneous or successive production of both these lesions, however, in the same animal, produced striking effects. This seems to show that while each of these injuries may in itself cause some impairment of hemolysin production, only a combination of both raises this to the point of total inhibition of hemolysin formation. The assumption seems inevitable that the deleterious effect of saccharated iron oxid injections is dependent on a diminution of normal hemolysin production.

The authors conclude that the liver is an essential necessity in the production of icterus, while the spleen and capillary endothelium are of negligible importance for this purpose. On the other hand, the presence of an intact capillary endothelium is a paramount necessity for the production of hemolysins when the supply of normal hemolysin has been exhausted.

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#### **Further Studies on Eosin Hemolysis.**

*Carl L. A. Schmidt and G. F. Norman, J. Gen. Physiol., 4:681, July 20, 1922.*

It has been observed by other workers that eosin hemolysis can be prevented by the addition of tyrosin, tryptophan, and proteins which contain these amino-acids. Since the publication of these results the authors noted a striking similarity between the substances which protect red blood-cells against hemolysis by eosin and the substances which react with the Folin and Denis phosphotungstic-phosphomolybdic reagent to give a characteristic blue color. Experimental work was accordingly undertaken to determine whether inorganic reducing substances in addition to tyrosin, tryptophan, and proteins which contain these amino-acids in the molecule could afford protection to red cells against eosin hemolysis. In each of a number of small test-tubes, 0.5 c.c. of a 5% saline suspension of red blood-cells (ox or sheep) was placed and to each 1 c.c. of a 1:10,000 dilution of eosin in salt solution was added. The substances to be tested for protective action were likewise made up in normal saline solution in different concentrations, and the reaction was adjusted to approximate neutrality. The tubes were placed in direct sunlight for 30 min. and after exposure they were immediately placed in the ice-chest. The tubes were inspected at the end of several hours to determine the amount of lysis which had taken place. The experimental results indicate that inorganic reducing substances afford marked protective action to red blood-cells against eosin hemolysis. Marked protection was shown by each of 2 preparations of histidin, as well as by skatol and tryptophan. Valin, serin, prolin, creatinin, and cinnamic acid afforded no protection.

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**Errors in Analyses of the Blood and Other Organic Fluids, Caused by Water Adhering to the Syringe and Tube.**

*César Clariá, Semana méd., Buenos Aires, 29:969, June 8, 1922.*

About 70% of blood specimens sent to the laboratory for analysis are laked on their arrival. The serum rarely retains its yellow color. This cannot be due to hemolytic microorganisms, under the aseptic conditions now obtaining. The hemolysis can be due only to the admixture of water with the blood at the time of its collection. This is attributable to the practice of boiling the syringe for the purpose of sterilization. As much as 0.3 c.c. water may be retained in syringe of 10 c.c. capacity, and 0.6 c.c. in the tube. Even these small quantities affect the result when the amount of the fluid to be tested is small. In Clariá's experiments the amount of urea in serum collected under proper conditions was 0.6 gm. per thousand, that in laked serum, 0.528 gm. per thousand. The amount of albumin in properly collected cerebrospinal fluid was 0.2 gm. per thousand, that in fluid withdrawn into a moist tube, 0.16 gm. per thousand. These figures indicate the necessity of thoroughly drying all syringes and tubes before withdrawing fluid to be subjected to delicate tests.

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**Buffer Systems of Blood Serum.**

*Edward A. Doisy, Emily P. Eaton and K. S. Chouke, J. Biol. Chem., 53:61, July, 1922.*

In these experiments the authors attempted to analyze the sources of alkali by which the blood combines with increasing amounts of carbon dioxid and to estimate the quantitative contribution of each. The plan was to determine the gain in serum bicarbonate on equilibrating fully oxygenated, defibrinated blood with 20, 40, and 60 mm. tension of carbon dioxid. By determining also the gain in bicarbonate of separated serums similarly equilibrated with increasing tensions of carbon dioxid, there is obtained the effect of the self-possessed serum buffers. As indicated by Van Slyke in his treatment of the data on Joffe's blood, the difference between the 2 sets of values (for true serum and separated serum) represents the buffer action of Type 1, which is due to the presence of the corpuscles. The determination of chlorids in the true serum shows the amount of base liberated from NaCl by the migration of HCl.

The serums were also analyzed for inorganic phosphates and from this one may calculate the relative amount of base furnished by phosphate and protein buffers, the self-possessed buffers of the serum. The material used consisted of the blood of 4 dogs and of 2 men. The tabulated and graphic results show that between the pH range of 7.45 and 7.25, the base furnished for the increase of bicarbonate in serum comes from the sources indicated (mean results): (1) "Self-possessed," nonmigrating serum buffers, 16%. Of this, phosphates supply 1-3%. (2) "Loaned" buffer, due to presence of corpuscles, 84%. Of this migration of HCl into corpuscles liberates 80%. The remaining 3% is probably liberated from the salts of other acids, by migration of the latter into the corpuscles.

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**Studies on the Nature of Nonspecific Protein in Disease Processes. IV. Blood Fragility, Reticulation and Blood Chemistry.**

*Roy Mark Greenthal and George Maxwell Brown, Arch. Int. Med., 39:99, July, 1922.*

There was a slight increase in the fragility of the erythrocytes during the protein paroxysm, but no change was noted in the percentage of reticulated erythrocytes. There was a moderate rise in the urea and total nonprotein nitrogen of the blood at the height of the fever resulting from the protein injection. The alkali reserve of the blood fell moderately after the foreign protein injection; this fall was of short duration, and a normal reading was soon obtained. During the protein shock the total blood lipoids decreased, which was perhaps more marked than that which was found in fasting subjects not receiving the protein. There was a slight rise in the blood sugar curve (Folin and Benedict) at the height of the reaction following the protein injection. The authors believe that the so-called protein shock and anaphylactic shock are different phenomena.

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**A Micromethod for Nonprotein Nitrogen Using Two-Tenths of a Cubic Centimeter of Blood.**

*C. M. Wilhelmj, J. Lab. & Clin. Med., 7:622, July, 1922.*

Blood is obtained from the lobe of the ear or the finger, sufficient amount being secured by one puncture. The blood is drawn into the blood pipet up to the 0.2 c.c. mark and immediately discharged into a small tube graduated at 2.5 c.c., which contains a minute amount of finely powdered potassium oxalate. The blood pipet is rinsed twice by drawing distilled water up to the 0.2 c.c. mark and this is added to the blood; 5% trichloroacetic acid is added up to the 2.5 c.c. mark, a few drops at a time, shaking after each addition. At the end of 20-30 min. the mixture is filtered, using a filter paper just large enough to accommodate the whole amount; 1 c.c. of the protein-free filtrate is transferred to a slender, hard glass, digestion tube (1.1 cm.  $\times$  9.5 cm.), and 0.2 c.c. of the digestion mixture added. The digestion mixture consists of 1.5 c.c. of 10% copper sulphate solution, 15 c.c. of distilled water, 15 c.c. of concentrated sulphuric acid, and 1.5 gm. potassium sulphate.

The digestion is done over a microburner, the contents of the tube being kept in constant circular motion to prevent loss of fluid by "bumping." The color of the fluid gradually becomes lighter and finally becomes clear pale green, the boiling being continued for 2 min. after this change occurs. The solution is then cooled, and distilled water added, and the contents transferred to one of the ungraduated tubes of the aëration apparatus. The digestion tube is repeatedly rinsed with distilled water and these rinsings added to the contents of the aëration tube up to a volume of not more than 8 or 10 c.c., 0.5 c.c. of 0.1 n. HCl is put in the graduated aëration tube and the volume made up to 5 c.c. with distilled water. About 5 c.c. of fairly strong sulphuric acid is put in the remaining ungraduated tube and the apparatus connected with a filter pump. Just before the aëration is started, 2 pieces

of stick NaOH about  $\frac{1}{4}$  in. long are cut in half and added to the middle tube which contains the digested filtrate. The air current is then run at slow speed for 5 min. and rapidly for 20 or 25 min. longer. When the aëration is complete, 1 c.c. of Nessler-Winkler solution is diluted with an equal volume of water, and 1 c.c. of this diluted solution is added to the contents of the graduated aëration tube, and the volume made up to the 8 c.c. mark with distilled water. The Nesslerized solution is thoroughly mixed and transferred to the cup of either a Kober or Bock-Benedict colorimeter and compared with a standard solution. The standard is prepared by adding 1.5 c.c. of standard nitrogen solution to 75 c.c. of distilled water, in a 100 c.c. graduate; to this 5 c.c. of undiluted Nessler-Winkler solution is added, and the contents made up to 100 c.c. with distilled water. The comparison is best made with the standard cup set at 20.

Calculation.—Since the equivalent of 0.08 c.c. of blood is compared with the standard at a volume of 8 c.c. the equation becomes:

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \frac{30}{1} = \text{mg. N per 100 c.c. blood.}$$

In a total of 16 readings the micromethod gave higher results than the Folin method in 13 and lower results in 3. The greatest difference was plus 5.5 mg. This method is intended for clinical diagnostic purposes, not for research, where a higher degree of accuracy is desirable.

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#### **Distribution of Sugar in Blood-Corpuscles and Plasma.**

*W. Falta and M. Richter Quittner, Biochem. Ztschr., Berlin, 129:576, May 23, 1922.*

It has been shown that, under normal conditions, the blood-corpuscles in different animal species and particularly in man are free from sugar. In such investigations the most careful attention must be paid to the chemical analysis in addition to proper application of the agents arresting coagulation. Regarding the objections put forward by Brinckmann to the methods devised by Falta and Quittner, it is emphasized that with proper chemical analysis and under normal conditions, the blood-corpuscles are found sugar free either if coagulation be entirely prevented or if complete coagulation takes place.

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#### **The Lipoids of the Blood in Tuberculosis.**

*B. H. Henning, J. Biol. Chem., 53:167, July, 1922.*

The author wished to make a study of the blood lipoids in tuberculosis and in this paper reports observations made on 21 cases of advanced tuberculosis, mainly pulmonary. The methods used for the quantitative determination of the blood lipoids were those described by Bloor. Determinations were made only on the plasma. Cholesterol was determined on the blood extract both with and without saponification. The author's results show that cholesterol was uniformly low in the tuberculous blood when determined by the saponification method, but

normal when determined without saponification. Total fatty acid and lecithin were found to be within the normal range of values for these substances. The residual fatty acid of the blood was high and since there was no lipemia the presence of other forms of fatty acid combination than those ordinarily present is suggested.

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**A Colorimetric Determination of Blood Chlorids.**

*M. L. Isaacs, J. Biol. Chem., 53:17, July, 1922.*

Isaacs' colorimetric method makes use of the Folin and Wu filtrate, is rapid and employs a permanent standard. The reagents necessary are: (1) Silver chromate (red modification) best prepared by adding slowly 200 c.c. of a 5.5% solution of 10% silver nitrate. The silver chromate settles out rapidly. Drops of the chromate solution are added until there is a slight excess of chromate, which gives the solution a yellow color. After cooling, the silver chromate is thoroughly washed with distilled water and finally air-dried on a Buchner funnel. (2) Magnesium carbonate. (3) Ammonium hydroxid, 2%. Procedure: 10 c.c. of the Folin and Wu filtrate are pipetted into a small conical centrifuge tube (which has been previously cleaned with warm chromic acid solution). A pinch of magnesium carbonate is added to insure neutrality of the liquid. The contents of the tube are stirred with a thin glass rod. A small quantity (about 0.05 gm.) of silver chromate is introduced and thoroughly stirred into the solution. If all the red particles disappear more chromate must be added. After washing off the stirring rod into the tube, the tube is centrifuged for 2 min. The contents are then decanted through a small filter, into a 25 c.c. volumetric flask, great care being taken not to disturb the residue at the bottom of the tube. After the addition of 10 c.c. water to the tube, the centrifuging is repeated for 5 min. The contents of the tube are then filtered into the volumetric flask. The solution has a slight turbidity which is cleared up by the addition of 1 c.c. of a 2% ammonium hydroxid solution. Enough water is added to bring the solution to the mark. After mixing, comparison is made with a standard potassium chromate solution containing 0.4 gm. of the salt per liter. The value of this standard may be found by employing 5 c.c. of a 0.02 n. solution of sodium chlorid in place of 10 c.c. of blood filtrate. Since yellows are difficult to match, the colors can be viewed through a blue glass. With the chromate solution used above, the chromate being 99.4% pure, and with the colorimeter standard at 20, the following formula applies: 11,730 divided by the unknown reading equals milligrams sodium chlorid per 100 c.c. of blood.

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**The Estimation of Lipoid Phosphoric Acid ("Lecithin") in Blood by Application of the Bell and Doisy Method for Phosphorus.**

*F. S. Randles and Arthur Knudson, J. Biol. Chem., 53:53, July, 1922.*

In this method the reagents used are those described by Bell and Doisy. The procedure is given: 5 c.c. of whole blood or plasma are pipetted slowly into about 75 c.c. of alcohol-ether mixture (consisting

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of 3 parts of alcohol and 1 part of ether, both redistilled) contained in a 100 c.c. volumetric flask. The flask should be shaken during the addition to avoid the formation of large clots of the precipitate. It is then immersed in boiling water and shaken well to avoid overheating. As soon as the contents begin to boil the flask is removed, the mixture cooled to room temperature, made up to the mark with the alcohol-ether mixture, and filtered. The filtrate may be preserved in a well-stoppered bottle for a considerable period without deterioration.

For the determination, 10 c.c. of whole blood extract or 15 c.c. of plasma extract are measured into a large pyrex digestion tube (25 × 200 mm.), calibrated at 25 c.c. and containing 3 glass beads. The extract is then evaporated to dryness in a boiling water-bath. To the dry residue in the tube 6 drops of concentrated sulphuric acid and 1 c.c. of concentrated nitric acid are added. Both acids must be free from phosphorus. The mixture is then digested with a microburner, at first over a low flame, then over a higher flame until the nitric acid is driven off and the remaining sulphuric acid is perfectly clear. After cooling for 1 or 2 min. the sides of the tube are washed with about 5 c.c. of distilled water and 2 c.c. each of the molybdic acid solution and the hydroquinon solution are added. After mixing and allowing to stand for 5 min. 10 c.c. of the alkaline sulphite solution are added and the whole is well mixed. After 5 min. it is made up to the 25 c.c. mark with distilled water and compared in the colorimeter with a standard made by using 5 c.c. of the standard monopotassium phosphate (containing 0.03 mg. of phosphoric acid per c.c.) added to a 25 c.c. volumetric flask or tube graduated at 25 c.c. containing 6 drops of concentrated sulphuric acid. The color is developed in the same manner as described for the unknown. In making readings with the colorimeter it is necessary to empty the standard cup into the flask and refill it each time the solution in the other cup is changed. Otherwise, the solution in the unknown cup must be allowed to stand for 5 min. after being poured out before a reading is made. If the standard is set at 20 mm. the calculation will be made according to the following formula where S equals mg. of  $H_3PO_4$  in amount of standard used, R equals reading of unknown, and X equals c.c. of extract used:

$$S \times \frac{20}{R} \times \frac{20}{X} \times 100 = \text{mg. } H_3PO_4 \text{ per 100 c.c. blood.}$$

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### **The Relative Phosphorus Content of the Blood, Especially in Cancer.**

*Joh. Vorschütz and Jos. Vorschütz, Deutsch. med. Wchnschr., Leipsic, 48:861, June 30, 1922.*

The phosphorus content of the blood of 23 individuals (healthy persons and patients with cancer and other diseases) was determined by Neumann's method, and the phosphorus quotient estimated. This quotient is the proportion of the number of milligrams of  $P_2O_5$  in 10 c.c. blood to the number of millions of red blood-corpuscles per cu. mm. The earlier claims of Groblys to the effect that a phosphorus content of

more than 1.526 per thousand or a phosphorus quotient of more than 3.17 is always an indication of malignant tumor, are supported by these investigations, with the exception that cases of icterus, pneumonia, typhoid fever, tuberculosis, and acute disease must be excluded, inasmuch as the phosphorus content in these diseases may, under certain conditions, be extremely high. The estimation of the phosphorus content may be of great importance in the clinical study of carcinoma, as well as in differential diagnosis.

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**A Method for the Preparation of Crystalline Oxyhemoglobin.**

*Michael Heidelberger, J. Biol. Chem., 53:31, July, 1922.*

According to the author's method, oxalated or defibrinated horse blood or dog blood of known oxyhemoglobin content is centrifuged and the plasma or serum, and the layer of white cells are removed. The red cells are then washed 3 times with chilled 0.85% sodium chlorid solution. The cells are then rinsed into a flask with a few cubic centimeters of water. The vessel is cooled in ice-water, and a steady stream of a mixture of 4 parts of carbon dioxid to 1 part of oxygen passed in. Toluene is, meanwhile, added in amount equal to about one-seventh of the volume of corpuscles and the mixture is stirred with the glass inlet tube until it becomes pasty. Passage of the gas is continued for a few minutes, with vigorous stirring, after which the flask is fitted tightly with a rubber stopper and allowed to stand over night in the ice-box. The consistency of the resulting mixture depends upon various factors. If sufficiently thin it may be centrifuged with advantage in chilled tubes in a cold room, separating into an upper layer of toluene and cell fragments, an intermediate layer of clear solution, and a lower layer of oxyhemoglobin crystals. The 2 upper layers are poured off and the crystals drained in the ice-box on a chilled porous plate, the surface layer being renewed constantly as it dries out, in order to avoid possible conversion of the oxyhemoglobin into a form in which the oxygen is less reactive.

During this process a slow stream of carbon dioxid should be directed over the surface of the plate, otherwise a portion of the oxyhemoglobin will redissolve as carbon dioxid evaporates from the mixture. When drainage is as complete as possible, the oxyhemoglobin is scraped into a chilled mortar and ground to a smooth paste with sufficient ice-cold water to bring the final volume up to 3-3½ times (in cubic centimeters) the weight in grams of oxyhemoglobin present in the original blood. The thin paste of crude oxyhemoglobin is transferred to a beaker, set in ice-water, and titrated to minimum turbidity with normal sodium carbonate solution. The solution is next centrifuged and any toluene and cell fragments on top are removed through a capillary tube. The oxyhemoglobin solution is next chilled and a stream of the carbon dioxid oxygen mixture passed in until crystallization begins, after which the flask is tightly stoppered and set in the ice-box over night, when the crystals are sucked off on hardened paper in a Buchner funnel. The filtration is carried out in the ice-box, with a

slow stream of carbon dioxide passing into the funnel. For many purposes the oxyhemoglobin is undoubtedly sufficiently pure at this point. For further purification the recrystallization process is repeated.

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**On the Colorimetric Determination of Hemoglobin with Especial Reference to the Production of Stable Standards.**

*Edwin H. Terrill, J. Biol. Chem., 53:179, July, 1922.*

The author recommends that stock solutions of acid hematin be prepared as follows: Defibrinated or oxalated blood is centrifuged, the serum removed, sufficient water added for laking, and hydrochloric acid added to a concentration of 0.1 n. This is allowed to stand for 24 hours at room temperature for full color development. The solution formed is distinctly turbid, but by repeated filtration, preferably through hardened papers, a perfectly clear solution is obtained, having a concentration of 7-12% depending upon that of the unfiltered preparation. More concentrated solution may be prepared by pouring the solution into a flat dish and evaporating with an electric fan until the solution is of a syrupy consistency when it is filtered by suction. Evaporation is continued to the thickest solution that can be measured with a pipet. A known dilution is then standardized against a known acid hematin solution and the concentration of the stock solution calculated. It is then diluted to a convenient point, preferably not below 15%, and for later convenience accurately measured into 2 c.c. brown glass ampules.

A stable dry acid hematin protein powder of uniform color, from which standards may be prepared by weight, is made by centrifuging several hundred cubic centimeters of defibrinated or oxalated blood, removing the serum, and washing the cells 4 times with normal saline solution. The washed cells are mixed with an equal volume of distilled water, sufficient ether is added to produce complete laking, the mixture thoroughly shaken and allowed to stand 10 min. It is filtered or centrifuged to remove the stroma of the red cells, first diluting slightly with distilled water if too viscid. The filtrate is a clear dark red liquid still containing variable amounts of protein. This is removed by the addition of an equal volume of aluminum cream prepared according to the method of Tracy and Welker, followed by filtration. Alcohol is then added in small portions with constant shaking, until it constitutes about 20% of the volume. The solution is again filtered through a hardened paper. Air or oxygen is then blown through the solution until the hemoglobin is completely saturated, after which  $\frac{1}{2}$  volume of 0.25 n. HCl is added in small amounts with constant shaking. Instead of the turbid solution obtained by the addition of acid directly to whole blood, a very dark sometimes syrupy but perfectly clear product results. At least 24 hours should be allowed for full color development. Under no circumstances should it be warmed. Evaporation is next in order and when the consistency of a thick syrup is reached the solution is again filtered as before through a hardened paper. Evaporation to dryness is then completed as rapidly as possible, the mixture being frequently stirred. When thoroughly dry, the entire bulk of the preparation should be very finely powdered and thoroughly mixed. The yield from 500 c.c. of normal blood is about 40 gm.

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**An Efficient and Practical Method for the Counting of Red Blood-Cells.**

*Theo. R. Waugh, Arch. Int. Med., 30:216, Aug., 1922.*

Fifty c.c. sterile 2% sodium citrate in 0.85% saline is placed in a sterile 300 c.c. Erlenmeyer flask. To this is added approximately 5 c.c. blood freshly drawn from a vein of a healthy person and free from clot. As the blood is added the mixture should be agitated slowly and the cotton wool plug then replaced in the mouth of the flask, which is kept at room temperature with gentle shaking up of the settled corpuscles daily or oftener. At the end of 3 or 4 days, depending on the rate of evaporation, it will be noted that the color has changed from a bright to a slightly darker red, and if a drop is examined under the microscope, the cells will be found darker, smaller than when fresh and slightly crenated. There should be no clumping.

To the suspension, when the cells have attained this appearance, is added .200 c.c. Hayem's solution made up by this formula: Sodium chlorid, 1 gm.; sodium sulphate, 5 gm.; mercuric chlorid, 0.5 gm.; distilled water, 200 c.c. This must be filtered and perfectly clear. It is convenient if the suspension be now transferred to a tall, rather narrow glass-stoppered bottle or cylinder holding 500-1000 c.c. During the day the suspension is agitated; on the following day it will be found to have become light brown in color. The supernatant fluid is then siphoned off and replaced by fresh Hayem's solution. The cells are allowed to settle, the supernatant fluid is withdrawn and fresh solution is added. The suspension is then practically freed of the sodium citrate and the erythrocytes have become fixed. Under the microscope they appear small, crenated, brownish and quite highly refractile. The cells are now stained by adding 100 c.c. filtered eosin solution. The mixture is shaken up well from time to time, and the stain allowed to act for 24 hours, when the supernatant fluid is siphoned off and replaced by Hayem's solution. The excess of stain is thus removed; the process may be repeated if after settling the solution still contains much eosin. The suspension is now diluted with Hayem's solution so as to contain approximately 25,000 cells per cubic centimeter. Before counting it is best to transfer definite amounts to smaller glass-stoppered bottles. These are then brought to exact titer of 25,000 by making several careful counts with an accurate hemocytometer, fluid being added or withdrawn after settling, as required. The suspension thus prepared is absolutely stable. The blood, of which the erythrocyte count is to be determined, is added to the standard suspension in the proportion of 1:200.

For small amounts of blood an efficient procedure is to measure (after thoroughly shaking the suspension) exactly 1 c.c. into a test-tube. Dwarf test-tubes measuring  $10 \times 1$  cm. are a convenient size. The blood is obtained by finger or ear prick in the usual way, and is allowed to run by capillarity or is sucked by means of rubber tubing and mouthpiece into a pipet graded to measure 0.005 c.c. The end is then wiped off on a piece of gauze and the contents discharged directly into the 1 c.c. of suspension in the test-tube. The pipet is washed clear by drawing up and expelling the suspension; the mixture is shaken

thoroughly and a medium-sized drop transferred to a clean glass slide and covered by a cover slip. Bubbles should be avoided.

If the blood which is being examined has a normal erythrocyte count, that is between 4,500,000 and 5,000,000 cells per cubic millimeter, the corpuscles and standard suspension cells in the mixture will be in the proportion of approximately 1:1, and will appear in practically equal numbers in the microscopic field. For accurate enumeration it is necessary to count and record the exact number of each type of cell in several fields; a total of 1000 cells should be counted from each of 2 drops examined. The total number of each type of cell is computed, and by multiplying the sum of the fresh corpuscles by 5,000,000 and dividing by the sum of the standard suspension cells, the number of patient's red blood-corpuscles per cubic millimeter is quickly determined.

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#### **Rouleaux Formation of Red Cells in Various Types of Disease.**

*David Brewster Swift, J. Lab. & Clin. Med., 7:614, July, 1922.*

In view of the striking alteration in rouleaux formation under slight changes of environment in vitro, the author studied the effect of various types of disease on this phenomenon.

In this study, emphasis is placed upon the necessity of a standardized technic which permits quantitative measurements by varying the dilution of serum and cellular suspensions. The following routine was adopted. A few drops of blood were collected from the finger or ear in a Wright tube and centrifugalized. The serum was pipetted off and heated in a sealed glass tube for 30 min. at 60° C. For the red cells, a little blood was collected from the ear in 0.5% sodium citrate in physiologic saline contained in a graduated 15 c.c. centrifuge tube. The cells were thrown down and washed once with saline. As a rule, 20% suspension of cells was employed. Normal blood was collected at the same time as the patient's and all specimens were tested promptly because of the rapid deterioration which occurs at room temperature. Equal parts of heated serum and cellular suspension were measured with capillary pipet and mixed on a slide. From this mixture an ordinary hanging drop was prepared and kept at room temperature. Observations were made at the end of 5 min., 30 min. and 1 hour. Rouleaux formation often took place in 5 min. and, as a rule, did not increase after 30 min. Control examinations of normal blood were invariably performed and always yielded constantly uniform results.

In 7 out of 17 cases of Hodgkin's disease, rouleaux formation was completely lacking under conditions in which normal red cells formed intense rouleaux; 6 cases of myelogenous leukemia and 4 of the lymphatic type were studied and in all these cases rouleaux formation was depressed to a greater or less extent. That this is not due to the anemia which occurs in these diseases is shown by the fact that red cells of pernicious anemia cases formed rouleaux well. The 5 cases of typical pernicious anemia all gave entirely normal results; 5 cases of advanced chronic nephritis were tested and normal results were obtained both with the patient's serum and with the patient's cells. No



abnormal results were observed in any of 21 cases of infectious diseases tested during the acute stage. Of cases examined, 10 were of pulmonary tuberculosis, 4 of lobar pneumonia, 3 of diphtheria, 2 of measles, 1 of whooping-cough, and 1 of ulcerative endocarditis. Entirely typical rouleaux formation was obtained in 11 cases of advanced carcinomatosis and 3 cases of melanotic sarcoma.

From these results, it would seem that if any valuable information is to be gained by testing for rouleaux formation, some finer development of technic must be established.

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**The Biochemical and Biophysical Relations between the Erythrocytes and the Proteins of the Blood of Normal Persons at High Altitudes (Conclusion).**

*H. C. Fränkel-Tissot, Schweiz. med. Wchnschr., Basel, 52:635, June 22, 1922.*

With the aid of tables and curves, the author draws the conclusion that the globulin fraction preëminently plays the part of the sliding weight on the scale, in respect to the biologic and physical uniform erythrocyte-hemoglobin system. The observations on children and adults show an almost constant compensatory synergism of forces rubbing against each other in opposite directions. A mobilization of endocrine secretions, a changed manner of action in the adrenal economy, and an increase of the Traube-Hering waves from deepened respiratory excursions can be assumed. Muscular work, perspiration, and food ingredients play some part, especially in the effect of sodium chlorid and of minerals upon the carbonic tension of the blood, this acting on the ionic relationships, and these in turn acting upon the blood albumin. The curve of viscosity of the serum is unaffected by the erythrocyte and hemoglobin curves. The effect of the albumin-globulin sedimentation is recognized in the curve of the total blood viscosity by way of the serum viscosity. The combined method of studying the erythrocytes, hemoglobin, serum and blood albumin thus lays bare a number of new processes for the physiology and pathology of the blood at high altitudes.

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**The Azure Granulated Cells and Their Normal Qualitative Blood Picture (Arneth).**

*Arneth and Sahl, Münch. med. Wchnschr., 69:963, June 30, 1922.*

The normal blood shows a uniformity in regard to the number of the azurophil lymphoid cells, as well as in regard to the distribution of the number and size of the granules in the different kinds of cells. One-fifth to one-third of all lymphoid cells (lymphocytes and monocytes) have azure granules. From their investigations the authors draw the conclusion that the azurophil cells occupy a functionally unique position in regard to the other lymphoid cells. The granules can represent neither signs of age nor of degeneration. The size of the azure granules varies much more than that of the true granulations. The fine azure

granules characteristic of the monocytes, according to Nägeli, are not identical with the azure granulation of the lymphoid cells of Michaelis-Wolff. No clue can be found as to their origin in certain organs.

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**Changes in the Number of Small Lymphocytes of the Blood Following Ligation of the Thoracic Duct.**

*Ferdinand C. Lee, J. Exper. Med., 36:247, Aug. 1, 1922.*

In view of the importance of the thoracic duct as an avenue for the supply of lymphocytes to the circulating blood, the author has studied the effect of ligation of that vessel on the number of small lymphocytes in the blood stream. Young adult male cats were used for the experiments. White blood counts and differential smears were made from blood obtained from the ear of the animal. Counts were made on the day preceding operation, and on the morning of the day of operation. The latter was essentially an intrathoracic ligation of the thoracic duct and periaortic lymphatic plexus. Additional counts were made 5 hours postoperative and in the morning and afternoon of the following day. Examinations were then performed in the morning of the next 7 successive days, and after that on alternate days. At the end of 3 weeks the lymphocytes had usually returned to the preoperative level. Five animals were so studied.

From the data it was found that intrathoracic ligation of the thoracic duct caused an immediate fall of about 56% in the number of small lymphocytes in the peripheral blood, with gradual return to the preoperative level in about 3 weeks. There is no absolute proof that this gradual return took place *pari passu* with the establishment of the collateral circulation of the thoracic duct. It is definite, however, that the thoracic duct is an important avenue for the entrance of small lymphocytes into the blood stream, and that it is the pathway through which at least half of the small lymphocytes reach the circulating blood in the cat. The control experiments showed that although there was also a decrease in the number of small lymphocytes following operation without ligation of the duct, yet this decrease was only temporary, for the preoperative level was exceeded on the second or third day. Other cats which simply received ether anesthesia for  $\frac{1}{2}$  hour showed a temporary fall in the number of small lymphocytes.

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**The Mechanism of Production of Digestive Leukocytosis.**

*C. Ciaccio, Haematologica, Naples, 3:366, July, 1922.*

In a previous note, the writer, from his experiments upon fasting dogs, was led to admit, as plausible, the conception that digestive leukocytosis, whether or not preceded by leukopenia, is determined, not by the products of the digestion of the proteins, but by the action of the hydrochloric acid, leaving it an open question whether such action pro-

ceeds through the nervous, or (as many authors believe) through the humoral, route.

In the present note he reports experiments made upon human beings. He selected 12 individuals in perfect health to whom he administered, 20 hours after their last meal, 50-100 c.c. of pure hydrochloric acid at 4%. In every case an evident leukocytosis was observed, usually preceded by leukopenia, but there were individual oscillations in the intensity and duration of the leukocytosis.

As regards intensity, the increase oscillated between 20 and 67%, averaging 45%. As for duration, in the greater number of cases the maximum number of leukocytes was reached in 45 min., and subsequently decreased until, after 90-120 min., it returned to the first figure or one even slightly lower.

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### **The Peroxydase Reaction of Leukocytes in Acute Pyogenic Inflammation.**

*H. Ohara, Japan Med. World, Tokio, 2:164, June 15, 1922.*

The leukocytes, especially the polynuclear neutrophils, and the types immediately preceding them, are concerned in the elaboration of protective substances against bacteria and their metabolic products. During the struggle the cells are often injured and their protoplasm undergoes more marked changes than that of other tissue cells. Of the ferments produced by these leukocytes the author has made a special study of peroxydase.

Normal blood gives a green color reaction with tincture of guaiacol when hydrogen peroxid or ozonized oil of turpentine is added, but pus or blood showing a marked leukocytosis (20,000 or over) or the blood of myelogenous leukemia gives this guaiacol reaction without the addition of more oxygen. This does not apply to lymphatic leukemia even of a severe grade. This difference in the behavior of lymphogenic and myelogenic leukocytes Brandenburg has explained by chemical differences of the nuclear substance. Meyer attributes it to the presence of a ferment (an oxydase) in the myelogenous leukocytes. This ferment probably exists in the granules; among the various methods devised to demonstrate it, that of Sato has been found very satisfactory. The blood smears are dried in the air, then flooded with a freshly prepared 0.1-0.5% solution of copper sulphate for 10 seconds. Immediately a fresh solution of 0.2 gm. benzidin in 200 gm. distilled water, to which have been added 4 drops of 3% solution hydrogen peroxid, is applied to the smear and left for 20 seconds. On shaking, the second fluid appears blue near the surface of the blood film. When examined under the microscope, the erythrocytes and lymphocytes are unstained, the granules of the neutrophils and the myelocytes appearing light green. The cell protoplasm is pink, while the nucleus is not stained. Overstaining must be carefully avoided, and it is advisable to stain the specimens as freshly as possible. Ziehl's solution may be used for a counter stain, employing 1 drop of carbolfuchsin to 5-30 of water, or the concentrated stain for a moment, followed by thorough washing.

In most cases of acute pyogenic infection when blood specimens were thus examined, a decrease of the staining reaction could be noted.

With general and local improvement the reaction also improves. Apparently, there exists a certain parallelism between the severity of the infection and the degree of the staining reaction.

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**Estimation of the Cellular Elements of the Cerebrospinal Fluid.**

*E. Jakobsthal, Deutsch. med. Wchnschr., Leipsic, 48:867, June 30, 1922.*

It is requisite for the accurate differentiation of the lymphocytes that the acetic acid contained in the fluid to be tested should amount to 5%. The fluid for the test should therefore include: saturated alcoholic methyl-violet solution, 15 c.c., glacial acetic acid, 50 c.c., distilled water to 100 c.c. The amount of the methyl-violet solution may be increased to 20 c.c. if intense staining of the nucleus is desired. Small amounts of blood do not interfere with the accuracy of the cell count.

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**The Cellular Elements of the Cerebrospinal Fluid.**

*A. Levinson, J. Lab. & Clin. Med., 7:626, July, 1922.*

A study of cerebrospinal fluid shows certain types of cells in the various diseases of the meninges or of the brain proper. Recognition of these cells may be an aid in diagnosis and, occasionally, a guide in treatment. Not every stain used for blood cells will bring out the cells in the cerebrospinal fluid vividly. Methyl-blue was found to be the best stain for the cellular structure of the cerebrospinal fluid. Gram stain counterstained with methyl-blue has been most useful for morphologic study of both bacteria and cells. For those who cannot distinguish between violet and blue, it would be best to employ the Gram safranin stain for bacteria and plain methyl-blue for cells. It is most important to examine the cells soon after the fluid has been withdrawn. It is conceded that normal fluid contains only 4-6 cells per c.mm., all of the small lymphocyte variety. Any infection of the meninges produces an increased number of cells in the cerebrospinal fluid. The number of cells is not nearly as great in irritative conditions as in destructive processes.

Increase in cells caused by irritation of the brain or meninges may occur: (1) in the small lymphocytes in the tuberculous meningitis poliomyelitis and luetic involvement of the meninges; (2) in the large lymphocyte and fibroblast in chronic inflammatory conditions, e. g. luetic meningitis and brain tumor; (3) in the polymorphonuclear leukocytes, found in great numbers in the fluid in septic meningitides, in meningeal hemorrhage and, at times, in brain abscess; (4) in the endothelial cells and phagocytes, very numerous in meningococcic meningitis; (5) in the plasma cells in long standing processes, e. g. general paresis; (6) in erythrocytes from meningeal hemorrhage and in all acute inflammatory conditions; (7) in tumor and cyst cells, e. g. sarcoma cells, echinococci and actinomycotic granules; (8) in cells in all stages of degeneration, in all destructive processes.

## 1f. PATHOLOGY

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### **The Use of Pathologic Material in Small Hospitals.**

*John F. Kenney, Boston M. & S. J., 187: 195, Aug. 10, 1922.*

The author considers (1) the laboratory proper, (2) the director and laboratory workers, and (3) the work that can be done in a small laboratory. To start a laboratory requires only a small amount of money, a room with good lighting and proper plumbing, and it should be as close to the operating room as possible. A small animal house and a morgue for autopsies are essential, while light and ventilation are supremely important. The laboratory director should be a physician; his training is necessary for diagnosis and advice as to treatment. The director should perform all autopsies and should interpret all results and reports before they leave the laboratory. He should receive the best salary possible. The technician is always a problem but Kenney has found that nurses do especially good work because of their familiarity with office routine.

Extensive work can be done in a small laboratory, and is of the greatest importance. Wassermann tests should be made routinely. It is not difficult to have sheep, and amboceptor from one's own rabbits, and one's own complement can be made from guinea-pigs which do not require much care. Guinea-pig inoculations are used also in tuberculosis cases or in renal disease. Some of the other routine work done in the laboratory are blood typing for transfusion, blood urea and blood sugar determinations and tests for cavity fluids, renal functions, smears, stomach contents, stools, blood cultures, spinal fluids, and Widal's. Autopsies are so essential that everyone connected with the hospital should do his share in obtaining them.

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### **Biometric Studies in Pathology. I. The Quantitative Relations of Certain Viscera in Tuberculosis.**

*Raymond Pearl and Agnes Latimer Bacon, Johns Hopkins Hosp. Rep., 21:157, Fasc. 3, 1922.*

The authors have undertaken a highly technical statistical investigation to test the idea that a close relationship exists between the various important viscera, and that an upset of this balance will be found in connection with serious organic diseases. Taking 1100 autopsy records, they have calculated the ratios existing between the weights of the following organs: liver-heart, liver-spleen, liver-kidneys, heart-spleen, heart-kidneys, kidneys-spleen. The results were computed with all due biometric precautions and considered in the light of possible differences between the groups representing the 2 sexes, the white and colored races, the various ages, character of lesion, and state of activity at death. It was found that the functional balance of heart and spleen undergoes an orderly (linear) change during life. Due correction being made for this, it was next found that the various ratios measured are remarkably constant in both races and both sexes. This is in contrast, of course, with known racial and sex differences in the brain, skeleton, etc., and seems to indicate that the exact weight-relation of



the viscera to each other is of fundamental biologic significance, deeper even than race and sex.

Comparing next the active with the inactive tuberculous cases, it was found that the liver-heart and kidney-heart ratios were higher, the heart-spleen ratio lower in the persons who had died of active tuberculosis. More accurate information is believed to be afforded by comparing those subjects who were killed by tuberculosis with those who were attacked but fought it off, being killed only by intercurrent disease. Here again the ratios were altered from the normal. The general result is that fatal tuberculosis is associated with lowered heart-weight and increased spleen-weight. Whether the disease is the cause and the altered organ-relations an effect, or vice versa, biometry does not disclose, but the question is being investigated.

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**Fibroblasts and Reticular Cells in the Spleen of Experimentally Anemic Animals. Vital Staining with Trypan Blue.**

*Reitano, Haematologica, Naples, 3:413, July, 1922.*

In the spleen of animals rendered experimentally anemic and stained with trypan blue, the typical fibroblasts are differentiated from the reticular cells and the chromophile macrophages by the presence of rodlike substances, of blue-black coloring, and by the nuclear and plasmatic structure brought into evidence by the May-Grünwald-Giensa method.

Among these typical fibroblastic cells and reticular macrophages are to be found every kind of transitional forms. Fibroblasts and migrating cells at rest may therefore be reasonably regarded as reversible functional adaptations of the same hemohistoblastic cellular element. The writer found it impossible to discover any granulations stained with trypan blue in the neutrophile and eosinophile granulocytes.

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**Splenic Alterations in Infantile Leishmaniosis.**

*E. E. Franco, Haematologica, Naples, 3:303, July, 1922.*

Examination of the spleen in 10 clinical cases showed that their macroscopic aspect, save for the marked increase of all diameters, does not suffice to characterize the splenomegaly of leishmaniosis. The splenic tumor was due to the following facts: (1) the production, often striking, of hematic elements of the hemoglobinuric series; (2) congestion of the lacunas; (3) hyperproduction of the hematic cells of the lymphocytic series of the cords, often accompanied by that of the monocytic series and of plasma-cells; (4) adenofibrous modification of the reticulum of the follicles or cords of the pulp or of both together. This modification is often coincident with the disappearance of numerous follicular elements; (5) an abundance of large cells containing Leishman's parasites. In one spleen, to the hyperproduction of the elements of the hemoglobinuric series was united that of the granulocytic series, either passing through a hemocytoblastic phase or deriving directly from the hemohistoblasts. No appreciable modifications were noted in the

elastic tissue. In the megakaryocytes there was observed an inimical attitude toward the erythrocytes, the leukocytes, and the parasites, but no phagocytosis. The cells containing the parasites were those of Tigri's reticulum and of the reticulum of the follicles, and also the cells of the adventitia of the vessels and certain elements of the pulp.

The conclusions regarding the significance of the cells containing the parasites are: (1) The cells of Tigri's reticulum and those of the reticulum of the malpighian follicles (endotheloid cells) are hemohistoblasts (clasmatoocytes) with a nucleus similar to the monocytoïd, with a dense reticulum with close meshes. Invariably these 10 spleens affected with leishmaniosis gave rise, in mobilizing, to hemohistoblastic cells of the monocytic series without passing through a hemocyto-blastic phase. (2) These endotheloid cells of the splenic reticulum and their myocytic derivatives always have active phagocytic properties in presence of the leishmania cells, often even in presence of cellular elements either mature or immature, of the hemoglobin series. (3) The cells of the adventitia of the vessels, and certain of the cells situated immediately outside the lacunas of the pulp, are true hemohistoblasts which may give place to hemohistoblastic lymphocytes and more rarely (1 case in 10) to acidophile and neutrophile hemohistoblastic granulocytes; there are no hemohistoblastic cells with basophile granulations. The elements of adventitial origin have a spongiform nucleus. (4) The hemohistoblastic lymphocytic derivatives have phagocytic properties in the presence of the leishmanias; the granulocytes have none. (5) In the spleens examined, the endothelial cells of the bloodvessels and lymphatics, and those of the lacunas of the pulp, did not have any phagocytic power either against leishmanias or against other cellular elements. (6) The passage into the splenic vein of the hemohistoblasts of the reticulum or of the adventitia or their derivatives, many of which contained leishmanias, is to be explained by the irruption of a quantity of cellular elements in the lumen in the lacunas of the pulp, due to the constant breaking of their walls. (7) The same elements were found in the circulating blood, but in very limited numbers, because the greater part were arrested in the capillaries of the liver.

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#### **The Cellular Reactions of the Organism after Subcutaneous Injection of Fats and Oils.**

*Paul Wagner, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:290, 1922.*

According to the prevailing view the occurrence of lymphocytes in exudates or infiltrates is the expression of the existence of chronic inflammation, while the occurrence of polynuclears is observed with acute stimuli. For a number of years Bergel has sought to prove that the appearance of lymphocytes is a specific reaction to fatlike substances, while the exudates and infiltrates consisting of polynuclear leukocytes are produced by protein substances (for example bacterial metabolic products). Bergel supports his contentions by experiments on rabbits, guinea-pigs and mice, with injections of a 10% aqueous lecithin emulsion, 10% oily lecithin solution, almond oil, bone oil and olive oil into the thoracic and abdominal cavities and further by researches on the digestion of these and other fatlike substances by material containing

lymphocytes.. The author conducted analogous experiments and injected into mice, guinea-pigs and rabbits subcutaneously and intraperitoneally, 10% lecithin-olive oil, 10% lecithin emulsion, bone oil, cocoa oil wax, and various ointments and fat mixtures. Further, he placed small pieces of elder-pith soaked in these substances under the animals' skin and was enabled in this way to determine the quantitative proportions of the different blood-corpuscles. At intervals of 4 hours to 20 days cover-glass sections were prepared with the abdominal exudates, and the skin depots with their surroundings were excised and examined in paraffin sections and frozen sections. The author arrives at results differing from Bergel's. The latter found a slight increase of polynuclears in the first hours but after 10-12 hours the lymphocytes were also numerous and after one day they were predominant. The author on the other hand found that the initially abundant polynuclears disappear rapidly and the lymphocytes become predominant (in some experiments no leukocytes whatever appeared). No specific affinity of lymphocytes for fat exists. The accumulation of numerous lymphocytes on fat droplets, as described by Bergel, finds a purely physical explanation. Bergel finds that the lymphocytes form vacuoles and store fat in these, but according to the author the vacuoles are not constant and, on the other hand, are also present in the polynuclears. The author therefore rejects the assumption of a relation between lymphocytes and fat. That the occurrence of the lymphocytes is of special importance and that lymphocytes possess a function different from that of other leukocytes is evident, but Bergel's researches have not solved this question. His conceptions of the importance of his discoveries to the theory of tumors, of lymphosarcomatosis and of the Wassermann and miostagmin reactions are therefore untenable.

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**Studies on Enzyme Action. XX. The Protease Actions of Malignant Human and Rat Tumor Extracts at Different Hydrogen-Ion Concentrations and in the Presence of Various Salts.**

*K. George Falk, Helen Miller Noyes and Kanematsu Sugiura, J. Biol. Chem., 53:75, July, 1922.*

This investigation was begun to study certain enzymes which may be involved in malignant growths. The results in this paper are limited to the study of the proteolytic enzyme, and refer to the actions obtained with various human malignant tumors as well as the Flexner-Jobling rat carcinoma. The effect on the protease actions of different degrees of pH, the determination of the optimum pH, the change in action with time and with concentration of substrate and of enzyme material, and the effect of a number of neutral salts on the action at the optimum pH, were studied. The solutions and mixtures used for the enzyme experiments were obtained from human tumors and rat tumors. The proteolytic actions of the tumor extracts were studied by the formol and the Van Slyke amino-nitrogen methods on casein and on a peptone preparation. Similar results were obtained with the extracts from the two sources. Optimum conditions for action were found at pH 7.0. The general actions were similar to those of other protease preparations and could be formulated similarly. In the article are given detailed tabulated and graphic data showing the retardations exerted by various neutral salts and by mixtures of several salts.

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**So-Called Foam-Cell Tumors.**

*Else Petri, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:507, 1922.*

The foam-cell tumor described by the author deviates in essential respects from cases hitherto described. The tumor was found in the stomach at the autopsy on a 69 year old male cadaver that was received with the clinical diagnosis of carcinoma of the stomach. The tumor's form and consistency, the manner of its growth as well as its extension in the form of hepatic metastases, seemed to confirm this assumption. But a peculiar, opaque, white-yellow appearance of the neoplasm as well as of its metastases, at the surface as also at the surfaces of incisions, attracted particular attention. With very slight exceptions, it affected the totality of the neoplasm; and the principal tumor in the stomach as well as the nodules in the liver immediately recalled the character of xanthomatous structures. But an examination of fresh material failed to disclose the presence of the double refracting substance which is the chief characteristic sign of xanthoma. The white-yellow coloration was produced by remarkably large and everywhere equally well preserved cells with drop-shaped, strongly refracting content. The nature of the embedded substance had to be determined by minute histochemic investigations and elective staining methods. According to the histologic pictures, the destructive and metastasizing tumor is an epithelial neoplasm, of alveolar structure with partial glandlike arrangement and therefore an adenocarcinoma; having regard to the special morphology of the tumor cell it is a foam-cell carcinoma, while in respect to the pronounced white-yellow appearance of the primary tumor and the metastases, it is a xanthomatous carcinoma.

The histochemic examination of the drops embedded in the cancer cells showed the substance to be one with a large content of fat-pigments. Reviewing the entire results, it may be stated that the cancer cells do not contain lipoid substances in the wider sense (cholesterin, cholesterin esters) nor in the more restricted sense (cerebrosids, phosphatids), so that the deficiency of any double refracting substance, which was observed in the fresh preparation, was confirmed by staining methods. The transformation of the tumor elements into foam cells is therefore conditioned by the embedding of neutral fats in the perfectly preserved tumor cell. The original neoplasm has assumed an entirely new appearance from the storage of exorbitant masses of fat; the carcinoma has become a foam-cell tumor. The foam cells, as such, are morphologically similar in all respects to xanthoma cells but differ wholly from these owing to complete absence of a double refracting substance.

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**The Heterogenic Transplantation of Rat Carcinoma in the Brain of Adult Mouse and Pigeon.**

*K. Yamasaki, Japan Med. World, Tokio, 2:160, June 15, 1922.*

Shirai has succeeded in transplanting spindle-cell rat sarcoma into the brain of other animals and this method was used in the transplanting of epithelial tumors. The author transplanted rat carcinoma into the brain of mice and pigeons. The original tumor was about the

size of a pigeon's egg, firm, sharply outlined, adhering loosely to the deeper tissue, while the skin over it was freely movable; on section it showed crossing bundles of whitish connective tissue, holding a grayish white medulla or parenchyma, with small necrotic areas throughout. Histologically, it was a cylindric cell carcinoma, rich in parenchyma and poor in blood supply and interstitial connective tissue, with moderate tendency to hemorrhage and retrograde changes.

When transplanted subcutaneously into an animal of the same species, there were 80-85% of "takes," the new tumor reaching the size of a hen's egg in about 4 months. When transplanted into the brain, there were nearly 100% of "takes," though the growth was slower, and the greater part of the brain was replaced by the neoplasm. The portion of tumor for transplanting was taken from the periphery, avoiding as far as possible any areas of regressive changes; after maceration, it was injected into the brain of the next animal by means of an especially constructed trocar, through an opening made in the parietal bone, and at the same time the animal was inoculated subcutaneously with a portion of the original tumor. Altogether 65 mice and 48 pigeons were inoculated. In all these animals subcutaneous inoculation gave negative results; 64% of the mice inoculated in the brain gave positive results; among the pigeons there were many doubtful cases, but in 4 apparently positive results were noted on the fifth and seventh days of observation. The general health of the animals did not appear to be affected.

A week or more after inoculation, the tumor in mice appears as a grayish miliary focus diffusely infiltrating the medullary substance of the brain, the cortex being free from any gross changes. In this tumor mass there appear yellowish gray spots, indicating regressive changes. In pigeons no macroscopic lesions can be discerned; the microscopic findings after 5 days and 1 week indicate that proliferation takes place and the neoplasm extends into the brain substance along the perivascular lymph spaces. This growth is more rapid in mice than in pigeons, the tissue reaction in the latter animals being stronger, though it is not very marked in either species. These processes are generally more marked in the second generation of mice inoculated.

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#### **The Epithelial Genesis of Nevus Pigmentosus.**

*Eberhard Steden, Frankfurt. Ztschr. f. Path., Wiesbaden, 27: 64, 1922.*

The question of the origin of pigmented nevi which was studied by Unna in the nineties, has again come into the foreground owing to researches of Kreibich and of Bloch and his pupils. For the epithelial origin of nevus-cells these arguments have been submitted: (1) the cells' vesicular structure and the size of the nuclei; (2) the complete absence of connective tissue between the cells, which has however been disputed by other authors; (3) the situation of the cells in the epidermis immediately below the same, and the direct connection of the cells with the epidermis and its appendant structures; (4) proliferation of the epidermis and its appendant structures in the nevus region; (5) other malformations of the skin in the nevus region; (6) the detection of lipoids



in the superficial nevus-cells; (7) the detection of dopa-ferment in the nevus-cells; (8) the increase of the pyrenoid substance in the nucleus of nevus-cells. These observations are confronted by other authors' experimental results which are said to indicate the derivation of nevus-cells from the mesoblast: (1) the occurrence of fine connective tissue fibers between the nevus-cells or the presence of connective tissue nuclei between the nevus-cells; (2) the absence of the spinous processes and of epithelial fibrillation of the cells; (3) the proliferation of connective tissue, especially of the lymphendothelia in the nevus region; (4) the connection of the cell columns with the blood-vessels; (5) the diversified form of the nevus-cells with branches; (6) the lower large and upper small circumference of the nevus-cell heaps; (7) the similarity of the nevus-cells to proliferating serosa-endothelia; (8) the sharp demarcation of the cell columns and cell masses. The author collected postmortem material and examined the same systematically by various staining methods. A small part of the material was derived from operations. The nevi were situated on the most diverse parts of the body and were mostly flat or raised slightly from the body surface. Few were papillomatous. A part was strongly, another part feebly, pigmented. The majority came from persons between 20 and 60 years of age. On the strength of his experimental results the author states that a definite kind of cells occur in pigmented nevi which are designated "nevus-cells" and regarding whose origin great differences of opinion exist. These cells are large, polygonal, round to oval, and possess a large central nucleus. Owing to this nucleus they recall the basal cells of the epidermis but differ from these in the absence of protoplasmic fibers and spinous processes, as well as in their protoplasm's slight absorptive capacity for stains. The cells lie mostly in rounded heaps or irregular masses in the epidermis, or beneath it, or connected with it. Very often they also occur isolated in the connective tissue between the epidermis and the nevus masses. They are surrounded, partly singly and partly in heaps of several contiguous cells, by a fine, fibrous connective tissue network. In the interior of the superficial, and partly also in that of the deeper-seated nevus-cells more or less abundant brown pigment is found in the form of granules or small clumps. During incubation the pigment content increased markedly, as also on treatment of the sections with dioxyphenylalanin solution. In the latter treatment the granules assumed a blackish-brown coloration. In a few cases finely divided fat-drops were observed in the cells' interior. Between the nevus-cells and in the connective tissue surrounding the nevus heaps, more elongated and to some extent ramified, brown pigmented isolated cells occur, which are the chromatophores. The pigment of these cells also showed an increase after incubation and assumed a blackish brown coloration on treatment with dioxyphenylalanin solution. In the nevus region the pigment content of the epidermis is increased and very often shows ledge formation and irregular stratification. Hair rudiments, sebaceous glands and sweat-glands are generally entirely absent in the nevus region, or are little developed. All these alterations of the epidermis and of its appendant structures in the nevus region permit of no other explanation than that of a malformation of the epidermis at this area. The author summarizes the results of his investigation as follows: The pigmented nevi are to be attributed to a developmental disturbance of the epidermis during embryonic existence. This contention is justifiable

in the first place by other malformation phenomena of the epidermis and its derivatives, which are actually demonstrable in the nevus region. Recent researches of Meierowsky and his coworkers also point to such a derivation. According to them, the nevi are attributable to an alteration of the hereditary units in the germ-plasm of certain cutaneous areas. The new studies on the origin of the cutaneous pigment do not affect this conception. The pigment has no influence on tumor formation. Nevus-cells and chromatophores are to be referred to the same mother-cells, to embryonic ectodermal epithelial cells. From the increase of pigment in both kinds of cells from epithelial derivatives and the intactness of the cutis in incubation it may be concluded that the pigment is produced in the epidermis.

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**Melanin and the Brown Waste Pigment.**

*Hans Kutschera-Aichbergen, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:21, 1922.*

For many years a determination of the chemical constitution of the autogenous pigment has been attempted in various ways. Melanin is of the greatest interest chiefly because of its relation to the suprarenal glands, as is evident from the hyperpigmentation in Addison's disease. The "brown waste pigment" or lipofuscin (Borst, Hück) of the internal organs has not received the same attention. Although the production of lipofuscin seems to be, to a certain degree, a physiologic phenomenon of senility, all authors (Aschoff, Hück and others) emphasize that the formation of lipofuscin is influenced also by pathologic processes. Lipofuscin deserves consideration also because of its extensive occurrence. This pigment has been found in traces in most organs, but it occurs in relatively largest amount in the very organs which are of special importance to vitality and life, namely the heart, nervous system, suprarenal glands, testicles, epididymis and liver. The author studied the constitution of melanin and lipofuscin by microchemical methods. Chemical, enzymatic and comparative zoölogic and botanic researches justify the assumption that melanin of the skin is produced from a cyclic decomposition product of protein, namely a body closely related chemically to the oxyphenols, and particularly to tyrosin and pyrocatechin. These results are of special importance because adrenalin is also a pyrocatechin derivative. In addition to the relations of melanin to the skin, retina and in melanoma, relations of melanin to suprarenal function were also demonstrated. The autogenous brown pigments of internal organs are sharply differentiated from melanin. According to the prevailing teaching they are regarded as relatively unimportant "waste pigments" and are considered by Hück as fatty pigments (lipofuscin) in contrast with "true" melanin. On the strength of his results Hück justifies the assumption that lipofuscin and melanin are decomposition products of two inherently different substances (fat and protein). He remarks that for the fat-containing waste pigment, the origin from lipoid bodies may be assumed; possibly fatty acids are involved, which are converted into brown substances by oxidation. The author does not agree with this view. On the contrary, its inconstant behavior to all fat stains and its marked liability even to

the blue staining with Nile-blue (while the pigment itself, as is known, is characterized by extraordinary stability), rather prove that lipofuscin consists of two different substances presumably combined in varying quantitative proportions, namely, of a changeable fatlike substance and a very stable and resistant pigment carrier. The author sought to determine whether melanin and lipofuscin should be regarded as two entirely different substances, or whether a chemical relationship of the two pigments to each other and to adrenalin is more probable. The combination with lipoids represents neither a constant nor a characteristic peculiarity of lipofuscin, while true melanin may also bear relations to lipoids. The only remaining differentiating characteristic of the two pigments is their different behavior with silver nitrate and with bleaching agents, and according to Hück also the behavior toward fat solvents. The author's researches show that melanin as well as lipofuscin reduces silver nitrate, ammoniacal silver solutions and hydrogen peroxid. The reducing capacity of both pigments is associated with the pigment carrier and its colorless preliminary stage, or as expressed more briefly by the author, with the "pigment nucleus." The pigment nucleus of both pigments is resistant to most chemical procedures, insoluble in fat solvents and not depictable by fat stains. The pigment nucleus alone is, therefore, the carrier of the typical melanin reactions. All reactions characteristic for melanin can be demonstrated on the pigment nuclei of both pigments, the only difference residing in the reaction rapidity. The reactions take place rapidly with melanin, slowly with lipofuscin. The pigment nuclei of melanin and lipofuscin are therefore probably chemically identical, or at least closely related. Finally, the author believes it permissible to assume close chemical relationship of melanin and lipomelanin to pyrocatechin and hence also to adrenalin.

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**The Mechanism of Avulsion Cardiorrhesis.**

*A. von Albertini, Frankfurt. Ztschr. f. Path., Wiesbaden, 27: 385, 1922.*

The author describes a case of avulsion cardiorrhesis, which the history showed to be one of attempted suicide (fall from third floor). Pains in the region of the tenth right rib and the eighth left rib. Superficial respiration; deep respiration painful. No effusion in either pleural cavity. Some râle and crepitation in the right pulmonary lobe. Cardiac sounds barely audible but well palpable. Radial pulse not perceptible on the left and barely palpable on the right. Urine clear and without blood. At the vertebral column violent pain on pressure from the eighth thoracic vertebra to the sacrum. In the region of the lumbar and the lowest dorsal vertebra strong swelling of soft parts. No spinal curvature. Abdomen distended. Three fingerbreadths from the anterior superior iliac spine on the right was felt a knotty, elongated, irregular resistance ascending toward the costal margin. The region of this resistance was very sensitive to pressure, and embraced the entire right lower abdomen, extending slightly beyond the median line. The left iliac fossa was free from pain; the right was very sensitive to pressure, giving the impression of a fracture. The clinical diagnosis

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before autopsy was fracture of the pelvis and intestinal injuries. At autopsy, upon removal of the sternum there were seen on each side intramuscular hemorrhages in the fourth intercostal space; situs abdominalis unaltered. On lifting the intestinal loops, a very large retroperitoneal hematoma of the posterior abdominal wall was revealed. The heart was the size of the right fist. On the surface of the right auricle were a few subepicardial hemorrhages. Besides the lesions to be described the heart showed no peculiarities. At the lower margin of the entrance to the right auricle fairly extensive hemorrhages were found beneath the endocardium which followed the course of the musculature. The endocardium was very thin and nowhere visibly torn. At the base of the right and anterior pulmonary valve the endocardium was torn 1 cm. each way along the base. The site of the tear could not be probed; it had a hemorrhagic areola 5 mm. in width. The hemorrhage extended to the musculature. The left valve was intact. Neither the pulmonary artery nor the aorta showed any lesion. Pathologico-anatomic diagnosis: (1) oblique fracture of the sacrum; (2) compression fracture of the body of the second lumbar vertebra; (3) avulsion fracture of the second, third, and fourth right lateral processes; (4) large retroperitoneal hematoma; (5) transverse tear of the endocardium at the base of the anterior and right pulmonary valve; (6) horizontal tear of the pleura in the third and fourth right intercostal space and rupture of the pleura at the hilum of the right lung; blood effusion in the right pleural cavity; (7) hemorrhages in the anterior mediastinum, in the epicardium and endocardium at the base of the right auricle; (8) hemorrhagic spleen. Microscopical examination of the injured part of the pulmonary valve showed that the rent immediately below the valve attachment penetrated into the fibrous attachment of the arterial tube. The endocardium had a gaping tear, whose site was covered by a mass of fibrin, in which fibroblasts were already seen. The tear in the fibrous tissue contained abundant red blood-corpuscles. Transversely to the direction of the tear, corkscrew-like convoluted elastic fibers were seen lying free in the blood mass. Three forms of rupture are described in the literature, namely those from (1) bursting, (2) contusion, and (3) avulsion. In the present case the author believes an avulsion rupture to have been involved.

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**A Case of Nodular Myocarditis in Congenital Syphilis.**

*Wilhelm Dressler, Frankfurt. Ztschr. f. Path., Wiesbaden, 27: 56, 1922.*

While congenital syphilis, unlike acquired syphilis, is frequently manifested by changes in the internal organs, diseases of the latter being an almost regular phenomenon in congenital syphilis, syphilitic cardiac affections are rare both in congenital and acquired syphilis. In congenital syphilis extreme fatty degeneration of the cardiac muscle is relatively frequent and is probably not a direct result of syphilis, though nevertheless conditioned by it, as it can be traced to the disturbed nutrition of the syphilitic child. Various authors emphasize that extreme fatty degeneration of the heart is to be regarded as the characteristic sign of congenital syphilis. Much rarer than the nonspecific cardiac

changes are the specific affections related directly to syphilis. The latter are almost invariably diseases of the myocardium, while syphilitic endocarditis and pericarditis probably must be regarded generally as affections extending from the myocardium (Mracek). In the majority of cases syphilitic myocarditis does not occur as a true gummatous process but usually as an interstitial inflammation without the characteristic signs of syphiloma, and is either diffuse or more frequently in the form of circumscribed fibrous foci which, because of the nodular deposits in the cardiac muscle, cannot really be designated as gummas. In acquired syphilis these nodules, the same as the gummas, are generally situated in the wall of the left ventricle. Mracek describes them as small nodules of fatty white color and coarse consistency. The author observed a case in a 4 year old boy who died from pertussis pneumonia. The necropsy revealed multiple furuncles, acute intestinal catarrh, fatty degeneration of kidneys and liver, syphilitic osteoperiostitis of the femoral bones, and in the wall of the left ventricle of the apparently normal heart, below the annulus fibrosus, a nodular, coarse, grayish white deposit as large as a cherry stone, which caused the thickened whitish endocardium to protrude but did not extend as far as the heart surface. Microscopically the focus was comprised mostly of infiltrates, here and there enclosing remnants of muscular tissue, very few vessels, but extreme alteration of the small vessels within and even at a considerable distance from the focus. The vessels were obliterated or had a small eccentric lumen (sometimes several smaller lumina), and occasionally cellular infiltration of the vascular wall or of the perivascular connective tissue was present. The alterations were found in arteries and veins and were absent in parts of the myocardium remote from the focus. No giant-cells or necroses were found. The diagnosis of focal interstitial myocarditis with hypertrophic proliferation of the endocardium covering the focus was made. Spirochetes were not detectable, but a congenital syphilitic basis could nevertheless be assumed, above all, because of the characteristic affection of the long bones (diphtheria could be excluded) and, further, the vascular disease that extended to the neighboring vessels and was probably attributable to the same cause as the myocardiac affection. In numerous muscle fibers in course of degeneration the author found the nuclei altered in the manner described by Anitschkow, namely the chromatin substance in the form of a serrated longitudinal band. Such nuclei also occurred within the granulation tissue but transitions between muscle fibers and granulation cells were not found.

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#### **The Histopathology of Endocarditis.**

*Morris Dreyfuss, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:527, 1922.*

Dreyfuss opposes Hannemann's axioms regarding the histopathology of endocarditis: (1) that the verrucous efflorescences consist of fibrinous change of the valvular tissue and are therefore swellings and not superpositions, and (2) that leukocytes play no part in endocarditis but that all cells are traceable to valvular tissue. The author's researches extended to about 25 cases of even extensive endocarditic alterations.

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In addition to recent simple endocarditis there were also cases of ulcerative endocarditis (thrombotic) as well as recurrent endocarditis. Normal cardiac valves were examined as controls. Cases of thrombotic endocarditis with macroscopic evidence of this condition were excluded or employed as controls. The valves were fixed in Zenker formol with subsequent alcoholic iodine treatment and embedded in paraffin. The staining methods varied greatly in order to obtain many comparative pictures. The results do not coincide with Hannemann's. Even if the forms of thrombotic endocarditis with large thrombi be disregarded it is shown definitely that the thrombotic deposits from the blood have a material rôle in the verrucous growth of endocarditic process. At times the valvular tissue itself participates to a considerable extent in the formation of verrucas by means of swelling and proliferation.

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**Dissecting Aneurysm of the Aorta.**

*Fritz Schilling, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:336, 1922.*

Since Bostroem's basic work on healed dissecting aneurysm the possibility of a favorable termination of splitting of the aortic wall has become generally known. This "healing" of the dissecting aneurysm sets in when a return perforation from the aneurysm into the lumen of the aorta or its ramifications occurs. In such cases the aneurysm wall gradually becomes lined with a kind of new intima or even with endothelium. After a certain time secondary changes may occur in this newly formed lining similar to those observed in atherosclerosis of the aortic wall itself. A case specially characterized by this secondary sclerosis is described by the author. In a man, aged 61, who died from chronic nephritis and who had atherosclerosis and a recent and several earlier apoplectic attacks, there was found an old dissecting aneurysm of the thoracic and abdominal aorta extending into both iliac arteries. It arose from splitting within the layers of the media, namely in the thoracic part approximately in the center of the media, in the abdominal part more in the outer layers. About 1 cm. below the origin of the left subclavian artery the inner layers of the aorta were torn transversely and the cleft of the media beginning at that point emptied into the right iliac artery through a return perforation. The wall of the newly formed tube had a new intima (with endothelium), with changes like those in an atherosclerotic aorta as described by earlier authors. Regarding the site of the cleft the literature shows a preponderance of the ascending aorta, usually up to about 2 cm. above the aortic valves, next frequently at the level of the ligamentum arteriosum, the remainder being distributed over other parts of the aorta. What renal findings were stated pointed mostly to increased blood pressure. In other aortic fissures, chronic renal changes were also mentioned. Külls, Erb and Fischer observed aortic fissures following intravenous adrenalin injections in animal experiments. One of the causes of the production of dissecting aneurysm is therefore increased blood pressure; it is remarkable that the second probable cause, i. e. atherosclerosis and syphilitic aortitis, was rarely present in the reported cases. The author thinks that in his case, too, the plaques in the true aortic tube may have been a secondary process. For this reason he believes that the chronic rise

of blood pressure caused changes in the vessel wall; in the aforesaid animal experiments focal necroses of the media with subsequent calcification were also found. The author considers it improbable that trauma was the cause, but after the hypertonia and aortic changes this might be considered as an immediate factor.

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**Thrombo-Arteritis Pulmonalis.**

*Kurt Löwenstein, Frankfurt. Ztschr. f. Path., Wiesbaden, 27: 226, 1922.*

The right pulmonary artery was thrombosed, and a thrombus was found in parts of the left one; the foramen ovale was open and likewise thrombosed; no indications were seen of thromboses in any nuclear region; pulmonary arteries were free from sclerotic or atheromatous processes (excepting slight traces) as also at the aorta; no circulatory or pulmonary affections were present. Microscopic examination of pulmonary vessels ranging in caliber from the thickness of pins to that of thin lead pencils showed the lumen filled with connective tissue and elastic fibers interspersed in an axial direction with numerous endothelialized canals with elastic investment. These "recanalizing vessels" were derived from the small vessels situated in adventitious connective tissues. This severe injury affecting only the pulmonary arterial system the author attributes to purely hypothetical poisons acting in loco. He bases his view mainly on Anderes and Cloetta, who found a definite chemical substance,  $\beta$ -imidazoethylamin, capable of causing strong contraction of the pulmonary vessels in contradistinction to the vessels of the greater circulation. The disease picture of pulmonary thromboarteritis is a vascular change embracing the entire region of the lesser circulation. It is not related to arteriosclerosis and exhibits the picture of endarteritis obliterans, but with extremely numerous highly recanalized thrombi.

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**The Experimental Production of Periarteritis Nodosa in the Rabbit with a Consideration of the Specific Causal Excitant.**

*William H. Harris and Andrew V. Friedrichs, J. Exper. Med., 36:219, Aug. 1, 1922.*

The material employed in the present study was derived from a typical case of periarteritis nodosa coming to necropsy. The latter was performed 72 hours after death, the body having been kept for that time at approximately 0° C. The gross and microscopic lesions demonstrated the existence of the peculiar pathology of the arteries characteristic of periarteritis nodosa. From the gross standpoint, the greatest intensity of the process was in the vessels of the kidneys. This material was, therefore, chosen for the transmission experiments.

Transmission experiments were made: (1) After searing the organs the gross lesions of the kidneys, consisting of several nodules of various types and sizes were dissected out with sterile instruments and fragments cultured in plain, glycerol potato blood, dextrose agar, and Löffler's blood serum. No growth was detected after 1 week. Portions of the nodules were ground in a sterile mortar in sterile normal saline

and after the coarser particles sedimented out, 2 c.c. of the finer emulsion were injected into the ear vein of 2 full grown rabbits, A and B. A died 2 months later. Rabbit B was killed 18 days later after drawing blood from the heart for inoculation and cultural purposes. The aerobic, anaërobic, and Smith tissue cultures remained sterile.

(2) Portions of kidney, liver, and heart of rabbit B were removed, macerated with sterile normal saline, and 2 c.c. of the supernatant fluid injected into the ear vein of 2 full grown rabbits, C and D: C died 1 month after inoculation; D died 6½ months after inoculation.

(3) Rabbit E was injected, into the ear vein, with 2 c.c. of a filtrate prepared from the organs of rabbit B of experiment 1 killed 2 months and 18 days after inoculation with human nodules. The filtrate was prepared from liver, spleen, and kidney, the suspension being passed through a Berkefeld filter N; this rabbit died 3 months after inoculation.

(4) Rabbit F was inoculated intravenously with 1 c.c. defibrinated blood from rabbit B of experiment 1, has survived thus far for 6 months, and is still under observation.

A consideration of the experiments, excluding the incomplete one, 4, shows that gross lesions, aneurysms and hemorrhages occurred in the liver and lungs of many of the rabbits. Those most typical appeared in the lung of rabbit E, injected with a filtrate obtained from an animal previously inoculated with emulsion of human nodules. In all the rabbits microscopic changes of some degree of intensity resembling those of periarteritis nodosa in man existed, consisting of infiltrations of adventitia and media and even intima with cells—neutrophils, eosinophils, lymphoid and plasma cells. Degeneration and necrosis of media, dilatation of vascular lumen, and thromboses occurred, with proliferative changes of the intima. The veins were only exceptionally affected.

The conclusions are drawn that periarteritis nodosa is a specific infectious disease which is transmissible to rabbits; that the lesions in rabbits are identical with those occurring in man, and consist of exudative and degenerative processes within the walls of smaller arteries in aneurysmal formations and thromboses; and that the microörganism inducing the disease is capable of going through a Berkefeld N filter and is therefore to be classed with the group of so-called filter passers.

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#### **Intimafibromatosis of Veins.**

*E. Hedinger, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:91, 1922.*

From a cursory examination of fibromas their structure and biologic behavior would appear to be simple but the whole fibroma question assumes a complicated character when a considerable mass of fibromatous material is subjected to investigation during a number of years. In the framework of the fibroma theory many points present themselves that are not easily reconciled with actual facts. In general the fibroma is designated as a tumor consisting of connective tissue cells and a fibrous matrix. The stroma is formed either by vessels only, or by vascular connective tissue. Macroscopically it is easy to separate diffuse fibromas or fibromatosis from circumscribed nodular or polypous fibromas. Growth is generally slow and expansive. This definition is

certainly correct for many fibromas. The analysis of fibromatous growth presents greater difficulty. The possibility of defining nodular fibromas, emphasized in the older textbooks and manuals, is frequently merely a theoretic postulate in no way corresponding to microscopical results. The same difficulty is met with in the attempt to prove that a tumor is involved which owes its enlargement merely to the expansive growth of a tumor germ and not to the circumstance that the adjacent connective tissue may also undergo secondary blastomatous proliferation. Strict proof of either conception is difficult because no definite conception of fibromatous growth can be arrived at owing to the close relationship between the histologic structure of the tumor tissue and the surrounding connective tissue. In the course of an investigation of a series of primary tumors the author met with a peculiar condition which revealed a possibility of fibromatous growth that is difficult to reconcile with the customary views. This case was one of fibroma of the back of the hand. The tumor consisted of medium-sized spindle cells with medium and mostly chromatin-deficient nuclei; between these everywhere was fibrillar matrix; the cells were nowhere so abundant that a fibrosarcoma could be entertained. Many of the spindle cells contained finely divided, partly double-refracting, drops of fat. A small number of small arteries were situated in the tumor having a distinctly marked media, a few small veins and several fissure-shaped lumina with high endothelium, on which followed directly connective tissue or also tumor tissue.

Sections prepared by Weigert's elastin method show abundant elastic elements in the outer parts; in the tumor's center they are rarer and usually short and in some of them 2 veins are seen whose lumen is generally found with difficulty in the form of a small fissure lined with endothelium; otherwise they consist of tumor tissue surrounded by a ring of elastic fibers and lamellas. The tumor tissue has the same structure as that of the entire tumor. The arteries in the tumor do not show this change. Frequently it may be observed that the elastic elements are bent outward before their destruction, which points to a proliferation of intima cells as the primary process, external growth following secondarily. The endothelium resists destruction. This applies also to the intimasarcomatosis described by the author years ago but in these there is also regularly found protrusion of the elastic fibers toward the interior so that the sarcomatous tissue proliferates from without inward. At the point where the ring is bent to the outside, a new penetration of the now internally situated tumor masses, toward the exterior, may be involved. Owing to this similarity the author terms the venous change in the present tumor intima-fibromatosis. The blastomatous growth stimulus which affected the connective tissue of the cutis also caused simultaneous, or chronologically slightly deviating, proliferation of the intima of the veins.

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#### Experimental Reactions of the Lung.

*A. Guieysse-Pellissier, Ann. de méd., Paris, 11:495, June, 1922.*

Reactions of the lungs to foreign substances may be studied after these have been injected into the trachea or into the veins. In regard to the first method, the substances which have been employed thus far by other investigators produce too violent reactions. The author for

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this reason prefers to use purified olive oil, which is absorbed after having given rise to a mild reaction in the alveolar wall. These investigations showed in the first place that the cells laden with coal dust, commonly found in the lungs, are not leukocytes, as is generally believed. After the absorption of oil it was seen that the superficial cells swell up and are cast off in the alveoli where they become dust cells. They may multiply there to such an extent as to entirely fill the alveoli and produce a pseudoneoplastic appearance, this being especially the case when the lungs have been exposed to the action of asphyxiating gases (catarrhal alveolitis).

When a suspension of tuberculous waxes, or of cod-liver oil, is injected intravenously, purely parenchymatous reactions without participation of epithelial cells are produced. Nodes are formed in the lungs which have the general characters of tubercles. They consist of a central group of large nucleated cells surrounded by a zone of lymphocytes. At first great quantities of polynuclear leukocytes appear, which are followed by eosinophils. Regarding the origin of these elements, it is known that the lungs possess a vast diffuse lymphoid system, which is scarcely visible under normal conditions, but develops considerably under the slightest stimulus, giving rise to lymphocytes and lymphoid cells. Although eosinophils are generally supposed to be generated in the bone-marrow, the author believes that they are formed in situ from polynuclear leukocytes, for the various steps of the transformation have been observed by him, and furthermore the number of eosinophils found in the blood appears to remain the same, whatever may be the abundance of these cells in the lungs. Experimental reactions of the lungs show, therefore, that this organ may mobilize its epithelial cells when it is attacked from the outside, or its lymphoid cells, to which are added eosinophils, when the attack comes from the inside. New organs are then created which resemble closed lymph follicles. The latter are defensive organs which have become permanent and hereditary, while those produced in these experiments are temporary. Tubercles are also similar organs of defense, but they are diseased and degenerate, while experimental tubercles are normal, healthy organs of reaction.

If bacilli of fowl-tuberculosis are injected into the veins of rabbits both parenchymatous reactions and catarrhal alveolitis are produced. The reaction does not take the form of isolated nodes but of vast patches undergoing degeneration. Epithelial cells multiply in great numbers in the alveoli but degenerate also. The remains of the alveoli become finally lined by a very regular cubical epithelium. This secondary epithelium, which probably represents bronchitic epithelium, forms an insuperable barrier between the external and internal masses of necrotic tissues. In these cases the defensive reaction has gone too far and the lung can never return to its normal condition.

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### **Experimental Production of Large Pulmonary Ciliated Epithelial Cysts.**

*Bernhard Fischer, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:98, 1922.*

An intimate relationship to tumor formation can at present be claimed for only 2 biologic processes, namely the embryonic anlage, and  
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typical regeneration. In a majority of tumors embryonic genesis is demonstrable. The essential foundation for tumor formation is, however, not the displacement of a tissue germ but the exclusion of a tissue complex from the physiologic relations to the whole body. Many tumors, however, such as Roentgen-ray carcinomas, paraffin carcinomas and others, cannot be attributed to an embryonic anlage. These are produced by continual injury to the epithelium leading to constant epithelial regeneration, which is influenced by the same injury, after a latent period lasting many years. Hence we find production of the tumor on the basis of disturbed regeneration. This applies also to internal organs. One-half of all primary carcinomas of hepatic cells are produced in connection with advanced cirrhosis of the liver; in chronic nephritis with strong regeneration, adenomas are produced at times. To make use of Virchow's obsolete stimulation theory for the purpose of explaining tumor formation, as was recently attempted by Fiebinger, is impossible, inasmuch as only a single tumor form develops even in uniformly stimulated cases and a very long interval elapses between the action of the stimulus and the formation of the tumor. On the other hand, the formation is comprehensible if the injury leads to regeneration, and it is this process which takes place in the latent period.

Although an autogenous cell, the tumor cell possesses properties that deviate from those of all other body cells; in the production of tumors the character of the cell must therefore undergo essential alteration. As the tumor is always produced on the basis either of an embryonic anlage or of a regenerative process, the experiment must intervene at these 2 points and principally in the latter, as the former can hardly be influenced experimentally at the present time. Years ago the author effected extreme, and partly cancerous, proliferations of grown rabbits' cutaneous epithelium by injections of scarlet oil. He selected, as the most sparing method, intravenous injections containing lipoid-soluble substances, whereby otherwise noninjurious fat-emboli were formed. He found 0.2 c.c. oil per kilogram rabbit a safe dose. The injection was always made in the auricular vein. The artificial fat-embolus may condition an anemic infarct of the lung but this does not occur generally if the oil is free from substances injurious to endothelium, though oil injection, even in the absence of injurious constituents, leads to slight endothelial injury, owing to continual repetition; its cells swell and surround the oil drops; they may become polynuclear and may contain one or more oil drops in their protoplasm which assumes a honeycomb structure ("foam-cells").

In order to obtain infarcts with certainty the author mixes various injurious substances with the oil, e.g. spermaceti with oil of camphor, alcohol with olive oil; or he alternates, daily, oil of camphor and a digalen mixture. After the appearance of the first infarcts no new ones are formed even if the injections be continued for months, probably owing to adaptation of the pulmonary circulation to the continual injury. At the infarcts' margins proliferation of the alveolar epithelium takes place from which macroscopically visible epithelial cysts may develop if the experimental procedure be a suitable one. For their production, therefore, the most suitable injection is granugen oil, either alone or mixed with other indifferent or active substances, such as olive oil, spermaceti, various alcohols, creosote oil and guaiacol. If the experimental

animal be examined at a later period after infarct formation the entire necrotic mass is found to be replaced by a large cyst which is lined by multiple-layered cylindric epithelium that communicates with small bronchioles and is entirely filled with air. In these experimental animals, also, no further infarcts are formed. The cysts are obtained most easily and surely with granugen oil without any addition (usually 0.5 gm. at intervals of 2 to 4 days). Admixture of other substances retards their development so that parts of the original necrosis are still found in the cysts. The removal of the necrotic mass is obviously effected by leukocytic activity (expectoration cannot be concerned as the narrow bronchioles collapse easily and therefore do not even permit the escape of inspired air from the cysts). Air enters the empty spaces that have been formed whereby proliferation of the epithelium, which gradually overlays the fissure walls, is promoted. Herein the alveolar as well as the bronchial epithelium participates.

As for the ciliated epithelium in the cysts, there can be no doubt that bronchial epithelium is found to participate energetically in epithelial proliferation. It is entirely conceivable that the bronchial epithelium grows only into the infarct regions and in this way forms the cysts. But it is seen that, simultaneously with proliferation of the bronchial epithelium, very strong proliferation of the epithelium of the entire adjacent alveoli sets in. These, too, form multiple-layered cylindric epithelium which does not differ in any way from proliferating bronchial epithelium and it must therefore be assumed that both kinds of epithelium participate in the lining of the air cavities and their bays and fissures. As alveolar epithelium has the same genetic origin as bronchial epithelium, a capacity for metamorphosing itself into cylindric epithelium by metaplasia is intelligible.

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**A Case of Epithelial Metaplasia and Metaplastic Carcinoma of the Right Main Bronchus after Influenza.**

*Berthold Meyer, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:517, 1922.*

Recently many authors (Teutschländer, Goldzieher, Askanazy, Oberling) have devoted attention to the question of epithelial metaplasia, particularly of the mucosa of the air-passages, and other related subjects. Askanazy observed metamorphosis of bronchial epithelium into stratified pavement epithelium in many cases of epidemic influenza. Teutschländer noticed the same in the rat's lung in bronchopneumonia and, in a new research, supplemented this observation by general considerations on the problem of metaplasia. Goldzieher described characteristic proliferations of the bronchial epithelium as a result of inflammatory affection of the air-passages, and interpreted these as proliferations of basal cells. At the same time he expressed the opinion that "the importance of such basal cell proliferations to the origin of tumors, especially of cancers, should not be underestimated." Regarding the frequency of tumor formation on the basis of metaplastic epithelial metamorphosis Askanazy has made justifiable reservations.

Nevertheless the author believes his case supports Goldzieher's "fears" inasmuch as a distinctive bronchial carcinoma developed imme-

diately after influenza. The author inclines to the view that the carcinoma is attributable to metamorphic processes in the bronchial epithelium such as have been shown to follow various acute inflammatory processes. The case was one of latent tuberculosis of the right upper lobe followed by acute inflammation of the respiratory organs (epidemic influenza). The tuberculosis extended rapidly and was complicated by specific pleurisy with changes in the tracheal epithelium that must be regarded as a consequence of regenerative or metaplastic processes. Proceeding from these epithelial formations a malignant tumor developed and extended particularly toward the hilum of the lung where, by constricting individual bronchi, it led to bronchiectases and caseous pneumonia. This tumor, which was the true cause of death, was composed of the most diversified epithelial formations and must be designated a metaplastic carcinoma. Terminal symptoms were edema and hypostatic pneumonia of the lower parts of the lung. The parallel occurrence, in this case, of two similar processes in the trachea and in the tumor arising from it, may not be without special interest; a common feature of both processes was what is generally termed metaplasia. Part of the changes in the tracheal epithelium could be regarded as the result of regenerative processes, for instance, the replacement of injured and partly desquamated ciliated epithelium by irregular series of cylindric epithelium with distinct relationship to basal cells. The occurrence of "epithelial islands," to be regarded as transitional epithelium, was probably also related to some regenerative process. The author conceives that in such cases the agent which induces the imperfect or atypical regeneration (metaplasia) continues to act, or at any rate induces simultaneous infiltration (chronic inflammation). Thus the author concludes that metaplasia involves metamorphosis not merely of the epithelium, but also of the mucosa. The metaplasia probably originated in direct connection with influenza. Owing to the wide distribution of influenza it is at once surprising and gratifying that more cases of the kind have not come under observation.

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**Artificial Hemorrhagic Pulmonary Infarct.**

*E. Meneghetti, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:447, 1922.*

Hemorrhagic pulmonary infarct can be produced regularly by intravenous injection of colloidal  $\text{As}_2\text{S}_3$  or of  $\text{Sb}_2\text{S}_3$ . As soon as these colloidal solutions come in contact with the blood, there is a rapid transition of the sulphid from the dispersive phase into the granular phase, of hydrosol into hydrogel, in the solid amorphous condition (flocculation), and as a result of these changes an indefinite number of small emboli are formed which obstruct numerous capillaries and also a number of small pulmonary arteries. Later, owing to the slight but important solubility of the sulphids, toxic products are formed around each embolus and cause a pathologic lesion of the capillary walls. Under such conditions hemorrhagic pulmonary infarct is always produced. For the same reasons the introduction of colloidal  $\text{HgS}$  causes extensive embolism of the pulmonary capillaries, but owing to the slight solubility of  $\text{HgS}$  the concentration of the toxic products in solution

is too low to cause sufficient alteration in the capillary walls, and the infarct is not produced even when large amounts are introduced. But HgS is not absolutely chemically inactive. Besides substances that are chemically inactive (paraffin) and the chemically active emboli ( $\text{As}_2\text{S}_3$ ) there is a series of emboli with a chemical activity midway between these. Hence either the typical hemorrhagic infarct or lesions merely approaching the infarct but without all of its characteristics, will be produced. It appears, therefore, that experimental hemorrhagic infarct of the lung is a capillary phenomenon as was maintained by Cohn. The chief factor in the pathogenesis of this infarct is the toxic lesion of the capillary walls. If it be borne in mind that a lesion of the numerous capillaries with resulting thrombi may be produced in an inflammatory process of the pulmonary tissue, it may be assumed that under such conditions a hemorrhagic infarct may be formed in the absence of emboli.

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**Punctiform Calcifications of the Renal Cortex.**

*Kurt Oppenheimer, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:368, 1922.*

In addition to the familiar calcareous metastases, infarcts and incrustations of the kidney, there are references in the literature (since 1900) to punctiform calcareous bodies of the renal cortex (Baum). These are macroscopic white spots, which were formerly taken for calcified glomeruli, but have been mostly found to be small calcified cysts. The author investigated 7 cases in accordance with Baum's methods, employing alcohol-proof material in order to obviate any solution, no fixative, paraffin serial sections, staining with Röhmer's hematoxylin and a few with counterstaining according to von Gieson. The calcium reaction of the fresh section twice showed pure calcium carbonate and 5 times a mixture of calcium carbonate and calcium phosphate. The calcium consisted of small granules situated in cavities; the latter either resembled the capsular cavities or they were at times considerably smaller than these, but also attained double their size, and some had a very irregular shape. The serial examination showed several such cavities united to form a cavernous system. They were situated with remarkable frequency close to intact glomeruli and even encroached on their capsule cavities at times. After decalcification of the section a colorless granular mass remained, frequently a fine meshy framework. Contrary to Baum no remnants of glomerular loops were ever found, nor any cellular elements. The matrix consisted, as shown by comparisons with the convoluted tubules, of coagulated albuminous masses, and the glomerulus-like cavities are derived from dilated convoluted uriniferous tubules. The calcified substance is the tubular content. The described cavities occur also in calcium-free kidneys. They are not cysts but cystlike dilated uriniferous tubules. The cause lies in congenital developmental disturbances, indicated likewise by other signs in the examined kidneys, such as fetal lobulation, and once by a medullary fibroma. Calcification is a result of advanced age: in younger individuals it is rarer and it never occurs in juveniles. Possibly chronic disturbances also play a part. In most cases there was also atheroma-

tosis of the large and medium arteries and in one, in which this was absent, a colloid goiter with calcification.

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**The Behavior of Cholesterols in Blood and in the Kidneys and the Pathologico-Anatomic Changes in Cholesteroluria.**

*Lothar Tietz, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:353, 1922.*

The literature shows that, in nephritides (particularly chronic), the cholesterol content of the serum is increased, while it is diminished in renal atrophy; the slower the atrophy, the greater the diminution in cholesterol. In severe uremia it is also diminished. Doubled refracting lipoids in the urine indicate kidney diseases. Opinions still differ, however, as to whether inflammatory and degenerative kidney changes are distinguishable in this respect. Double refracting lipoids in the kidney are always to be regarded as a sign of degeneration but single refracting lipoids may correspond to a reversible change. According to Löhlein double refracting lipoids never occur in fatty infiltration. The author determined the cholesterol content of blood, urine and kidney substance colorimetrically by the chloroform method (Authenried and Fock). The kidney was also examined microscopically. He found that while no definite relation exists between the serum and the urine cholesterol, there is such a relationship between the urine cholesterol and fatty degeneration of the renal epithelium (in the convoluted uriniferous tubules of the first order). The epithelium that has undergone fatty degeneration becomes loaded with cholesterol derived from the blood and is flushed out with the urine. An injury to the kidney parenchyma, namely fatty degeneration of the convoluted uriniferous tubules of the first order, must always be present when cholesterols appear in the urine. What rôle an increase of blood cholesterol plays in this transfer to the fatty epithelium and to the urine it is difficult to decide. At any rate hypercholesterolemia alone is unable to effect this; even with high blood cholesterol values, without kidney injury no cholesterol enters the urine, whereas in nephropathy considerable cholesteroluria may be present with a low serum cholesterol content. The author was able to show in the microscopic kidney sections that with sudan and scarlet staining double refraction is strongly diminished or entirely abolished in about half the cases. In staining with Nile-blue sulphate double refraction was almost invariably well maintained. But the anisotropal substances could be best recognized in the unstained section.

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**The Presence of Bacteria and Formed Elements in the Urine of Rabbits.**

*Henry F. Helmholz and Frances Millikin, J. Lab. & Clin. Med., 7:589, July, 1922.*

So-called spontaneous nephritis in rabbits has been recognized by investigators who employ these animals for experimental purposes. Thus, Helmholz and Beeler, in studying urinary infections in rabbits as

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induced by *Bacillus coli*, encountered one rabbit with naturally acquired pyelocystitis. The purulent urine, when cultured, yielded the *B. coli communis*. This was the only rabbit of a large series examined, whose urine contained bacteria, pus, or other pathogenic elements. Upon prosecuting these experiments after the war, it was found, contrary to previous experiences, that the urine of a large number of rabbits contained pus, erythrocytes, and albumin or casts, associated with bacteria usually of the colon type. There was an apparent group incidence, with certain lots entirely free from renal disease as judged by the urinary examination. Animals with positive urinary findings, upon necropsy, disclosed characteristic lesions in the kidney.

The urine of 99 rabbits was examined; pus was found in 30, casts in 3, erythrocytes in 3, and colon bacilli, not accompanied by any of these elements, in 3 instances. The urine, obtained in sterile fashion from 63 of the 99 rabbits, was cultured in tubes of dextrose brain broth, and on blood agar plates, on litmus lactose agar plates, or on both. The urine of 43 of the 63 rabbits was sterile in all mediums used. The cultures from 16 yielded colon bacilli, in pure culture in 12, and mixed with other organisms in 4 instances; streptococci or staphylococci were recovered in 4 of the cultures; 11 of the 43 specimens of sterile urine contained pus, albumin, erythrocytes or casts. It was demonstrated that colon bacilluria associated with other abnormal findings occurs in rabbits more often than is commonly supposed. This introduces a serious source of error into experiments concerned with the production of urinary infections in rabbits, and therefore demands extreme care in the selection of healthy stock for both experimental animals and controls.

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**The Testicles in General Affections, with Special Reference to the Behavior of Interstitial Cells.**

*J. Berberich and Rudolf Jaffé, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:395, 1922.*

In children that succumbed to acute diseases the authors rarely found defective spermatogenesis but very frequently more or less increased interstitial cells. On the contrary the authors found defective spermatogenesis in old men with scant interstitial cells. In children succumbing to chronic diseases no constant results were obtained. In about half of the cases spermatogenesis was injured and the interstitial cells, especially in cases with cachexia, were frequently increased. In old persons more or less injury to spermatogenesis was observed, while the interstitial cells were only rarely distinctly increased. From this it appears that spermatogenesis is injured more in advanced age, in acute as well as in chronic diseases, than in childhood. On the other hand, increase of interstitial cells is more frequent in children. A relationship was demonstrable between definite diseases and definite testicular changes. Interstitial cells were particularly increased in children with acute and chronic diseases, in cachectic and in well-nourished patients. It is remarkable that in a large number of the cachectics the interstitial cells were increased. Underdevelopment in Kyrle's sense could not be observed at all, that is, it was not possible to distinguish the changes regarded as secondary from possible primary changes. Between

the "fat-margin zone" (lipoid content of Sertoli's cells) and the lipoid content of the interstitial cells there is a distinct interdependence: with abundant lipoid content of the interstitial cells the fat-margin zone is scanty, and vice versa. The authors were unable to draw definite conclusions from cases of fibrosis testis as this condition varies with different etiologic factors. In inguinal testicle interstitial cells were greatly increased with advanced injury of seminal epithelium, but isolated tubules with two or three layers of epithelium were always present. In one case of fatal chronic nephritis in which the healthy testicle was also examined, interstitial cells were also abundant in the healthy testicle. In the case of a patient who died one year after unilateral castration no changes of any kind were found in the remaining testicle. No indication could be obtained that the increase of interstitial cells is an expression of regeneration; increased interstitial cells without injury to spermatogenesis was found in cases in which no signs of regeneration were observable in spite of advanced injury. On the other hand, increase of interstitial cells was absent in advanced injury to seminal epithelium. Compensatory hypertrophy in Simmond's sense, namely, increase of interstitial cells in replacement of destroyed seminal epithelium, is quite conceivable from numerous observations, though not precisely demonstrable. Compensatory hypertrophy in the sense that increase of interstitial cells in the other testicle may set in after castration has not been observed in man. A trophic function of the interstitial cells is not excluded but the authors think that this cannot be the only function, as this is opposed by their results, by the conditions found in children and by the numerical disproportion between interstitial cells and seminal epithelium. Thus, in places in which spermatogenesis was completely extinguished, the interstitial cells were at times not only preserved but even increased and rich in lipoids. Secondly, such a function is also improbable from the proportion between the fat-margin zone and the lipoid content of the interstitial cells. In cases in which no more spermatogenetic epithelium was present, but only Sertoli's cells, the authors at times found in the latter a distinct fat-margin and increased interstitial cells rich in lipoid. The same objections apply to the assumption of resorptive activity. By this the authors do not maintain that trophic or resorptive functions do not occur, but it appears certain that another function must also be present. Such a function could, however, be only an endocrine one, not necessarily one that acts on the genital sphere, but possibly one with mutual relations to other endocrine glands. Possibly the chief importance of the interstitial cells lies in this function. However, the seminal cells may also possess an internal secretion, perhaps one influencing the genital sphere, though this assumption has not been demonstrable so far.

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**A Particular Form of Atresia of the Graafian Follicles of the Rabbit, Revealed by the Tannoferric Method.**

*A. L. Salazar, Am. J. Anat., 30:503, July 15, 1922.*

Among the atypical forms of follicular atresia observed in ovigenous ovaries in adult rabbits, follicles with a tannophile cord present a special interest because of their relations to hydropic atresia.

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The type in question is characterized by the existence in the interstices between the cells of the membrana granulosa, or the place that it occupied, of a long, thick cord, that becomes stained an intense black by the tannoferric method, which the author has elsewhere described. A series of plates shows the follicles in various stages of development. The cord appears as a heavy black line of great length, having so many flexures and circumvolutions that it is impossible to follow them. The cord gradually replaces the disappearing granulosa. There are some reasons for believing that it is the hypertrophied Slavjanski's membrane.

In the interstices between the cells, in the stained preparations, one often notes the accumulation of a liquid or pasty substance, having the appearance of homogeneous coagulation, and highly tannophile. The author gives the name of hydropic atresia to this enormous accumulation of a liquid substance in the interior of the ovigenous cord. It is very frequent in ovaries of ovigenous type; in those of follicular, atresic, and interstitial type, no hydropic ovigenous cords are found, but only rests. This hydrops is the only form of degeneration known in rests, large or small. The type of atresia of follicles with tannophile cord must be considered as a throwback of the specific atresic properties of the ovigenous cords and their rests. The formation of the tannophile cord is to be attributed to an aberration of the secretory processes of the epithelial cells, either of the follicle or of its rests. If this is so, it is easily understood how an atresic disequilibrium of these cells may cause atypical products. The tannophile cord is such a product, in the author's opinion. This movement transmitted to the follicles is not to be regarded as abnormal; the progressive disappearance of the cord in the follicles, as these grow older, shows, on the contrary, that we are dealing with a systemic phenomenon, that must be related to a complex still little studied, i.e. the reversion, even to the follicles, of the specific phenomena of the ovigenous processes.

If we admit the formation of the tannophile cord from an atresic modification of the secretory rôle of the epithelial cells, we must equally admit the participation of the same cells in the atresic hypertrophy of Slavjanski's membrane, a phenomenon almost constant in the post-chromatolytic period and even in the agonal period of nearly all types of atresia.

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### **Examinations of the Hypophysis in Experimental Guinea-Pig Diphtheria.**

*Ferdinand Wiethold, Frankfurt. Ztschr. f. Path., Wiesbaden, 27:251, 1922.*

Some references in the literature attribute to the hypophysis the responsibility for the failure of the circulatory organs in early death from diphtheria. One author (Abramov) reaches the following conception: In place of the diphtheritically poisoned suprarenal glands, the vasoconstrictor substance must be entirely supplied by the hypophysis. The pituitary secretion then increases to the utmost until the cells become completely exhausted and this emergency aid also fails. Grutzfeld, Koch and Boehnke, on the other hand, assume a direct injury to the hypophysis, the middle lobe of which is said to be especially sensitive to diphtheria toxins. As their results really conflicted, the

author subjects their researches to reëxamination. He compares the hypophyses of 36 guinea-pigs dying 1-10 days after administration of diphtheria toxin with 10 dying from experimental tuberculosis. The middle lobe of the guinea-pig hypophysis has two irregularly arranged cell forms, one with scanty protoplasm, large nuclei and several nucleoli, the other with a large, pale protoplasm body and nuclei only half the size of the former, but so rich in chromatin that other details are unrecognizable. Diphtheria has no influence on the form and numerical proportion of these two cell forms, as was found also in children dying from diphtheria in the early stage. The author therefore does not believe that change alterations of the middle hypophyseal lobe are regularly found in experimental diphtheritic infection of the guinea-pig.

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**SECTION 1—ANATOMY, PHYSIOLOGY  
AND BACTERIOLOGY**

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**SECTION 1. ANATOMY, PHYSIOLOGY AND  
BACTERIOLOGY**

**1a. ANATOMY AND PHYSIOLOGY**

(1a—239)

(1a—239)

**The Number and Variety of Constitutional Types and Individual Morphologic Combinations in Anthropology and in Medicine.**

*Fabio Frassetto, Riv. d. biol., Rome., 4: 329, May-June, 1922.*

According to the relationship between their longitudinal and transverse diameters, varies the "value" of the different parts of the body. Three varieties of the value are generally distinguished—small (micro), medium (meso) and large (macro). For the old anthropometric classification which considered the value of the trunk and that of the limbs, the author substitutes another, which takes into consideration also the value of the head. In a given individual any one of the 3 values of the trunk may combine with any of the 3 values of the limbs and with any of the 3 values of the head; the number of possible combinations that result gives the formula  $3^3$ , i. e. 27. If then, instead of considering the trunk in toto, we wish to consider the thoracic and abdominal cavities separately, we must, in order to obtain all the possible morphologic varieties, combine the 3 values of the 4 groups (thorax, abdomen, limbs and head); the figure resulting from this number of the morphologic combinations is  $3^4$ , or 81.

This classification, considering 3 values for each part of the body, may be called trinary. Designating the small, medium and large values, respectively, with the symbols 1, 2, 3 and writing one after the other the symbols corresponding to the value of abdomen, thorax, head and limbs, we obtain a number, composed of various figures, that characterizes exactly each determined constitution. Thus for example a subject indicated with the symbol 1321 is microsplanchnic (the first 1), macrothoracic (3), mesocephalic (2), and micromelic (the last 1). Wishing to be more exact still, we may subdivide each of the 3 values (micro, meso, and macro) into 2 subdivisions: minimum limit (micro-micro, micro, or hypomeso) and maximum limit (epimeso, macro, or macromacro). This classification, which takes into consideration for each part of the body 6 values, may be called senary. The author adopts it, taking into consideration 3 single parts of the body (the trunk in toto); the number of possible combinations is then  $6^3$ , i. e. 216. This classification has the symbols: 1 (micromicro), 2 (micro), 3 (hypomeso), 4 (epimeso), 5 (macro) and 6 (macromacro).

In order not to confuse these symbols with those of the trinary classification, which has other significations, we may write the letter S after the number composed of the figures that are senary symbols. A subject indicated with the symbol 156S is micromicrosplanchnic (1), macrocephalic (5), macromacromelic (6). One indicated with the symbol 234S is microsplanchnic (2), hypomesocephalic (3) and epimesomelic (4).

(1a—240)

(1a—240)

**The Musculus Mandibulo-Auricularis.**

*E. Cords, Anat. Anz., Jena, 56:53, Aug. 15, 1922.*

The results of the author's investigations regarding the occurrence of the musculus mandibulo-auricularis do not agree wholly with those of previous investigators. She is able to confirm fully, however, the statements of certain of these investigators as regards its positional relations as well as its origin and insertion. The muscle arises at the aboral (posterior) margin of the mandibula, at times nearer to the angulus, at others nearer the condylus. Ascending obliquely dorsad and slightly caudad, it is inserted in the majority of cases on the cartilaginous skeleton of the auditory meatus or of the pinna. Insertion on neighboring skeletal parts—the tympanum and the temporal articular surface—was observed only in Edentata (*Dasypus*, *Tamandua*, *Tolypeutes*). It is usually separated from the temporalis and masseter muscles by the dorsally ascending auriculotemporal nerve (from the third trigeminus branch), while in other cases it is partly or wholly perforated by the nerve, as in *Lutra vulgaris*, *Cricetomys gambianus*, *Myopotamus coypus* and *Chiromys* (Ruge). The muscle is innervated by a branch of the nervus auriculotemporalis. The author was nowhere able to trace direct facialis branches to the musculus mandibulo-auricularis. Bearing in mind the conditions of origin and insertion, the muscle's function will consist in a downward and forward pull on the cartilaginous skeleton of the ear and it will act as a depressor of the mandible only in forms in which it trends toward the tympanum or to the temporal articular surface, i. e. in *Dasypus*, *Tamandua* and *Tolypeutes*. Despite its very extensive distribution among mammals, the occurrence of the musculus mandibulo-auricularis in lower vertebrates has not hitherto been demonstrable. On comparing the musculus mandibulo-auricularis with the musculus detrahens mandibulae (found only in Monotremes), the author found that the only noteworthy factor in the behavior of the mandibulo-auricularis as against that of the detrahens is the innervation of the former by a branch of the trigeminus. No genealogic conclusions can be drawn from the behavior of either muscle. On the other hand, the wide distribution of the mandibulo-auricularis among mammals furnishes further support for the theory, propounded in numerous publications by Gaupp, of the neoformation of the mammalian temporomaxillary articulation orally from that of nonmammalia.

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(1a—241)

(1a—241)

**The Innervation of the Sternocleidomastoid.**

*Victor Richer, Bull. et mém. Soc. anat. de Paris, 92:220, May-June, 1922.*

The author's descriptions are based on an available total of 24 specimens. In 90% of the cases, the spinal accessory innervates the sternocleidomastoid. In 80%, the spinal accessory anastomoses with the cervical plexus. In 10%, the anastomotic loop is double. The situation of the anastomosis within the muscle may cause it to escape notice. The anastomosis occurs with the second and not with the third cervical. The anastomotic fiber proceeds directly from the second cervical, and not even from the loop between the second and third

cervicals. There are 2 usual types of structure. In 50% of the cases, the branch of the eleventh nerve distributed to the trapezius quits the anastomosis between the eleventh nerve and the second cervical. This branch may be reinforced by fibers from the second cervical. In 18% of the cases, the trapezial branch of the eleventh nerve is given off before anastomosing with the second cervical. Reinforcement may occur as in the other type. The variation in the trapezial branch of the spinal accessory is particularly interesting. The origin of the branch may be high or low. The nerve received by the trapezius is normally of 2 types. The first consists of the branch from the eleventh nerve, reinforced by the second cervical (occurring in 12.5% of the cases). The second type, present in 12% of the cases, consists of a branch from the cervical plexus, with which the eleventh nerve anastomoses without direct distribution to the trapezius.

(1a—242)

(1a—242)

**The Anatomy of the Nerves of the Velum Palati.**

*Jean Rousset, Bull. et mém. Soc. anat. de Paris, 92:225, May-June, 1922.*

The well-known branch from the lower maxillary, distributed to the tensor palati, is not discussed. Otherwise, the muscles of the soft palate are innervated by the posterior palatine nerve, by fibers from the pharyngeal plexus and sometimes directly by the glosso-pharyngeal. Almost from its origin, the posterior palatine nerve occupies the groove in the postero-inferior part of the pterygomaxillary fossa on the upper part of the external surface of the vertical palatine plate, between the maxillary tuberosity in front and the anterior border of the pterygoid behind. During a course of about 2 mm. in this groove, the nerve, accompanied by an arteriole derived from the descending palatine artery, is in contact with the anterior and middle palatine nerves and the descending palatine artery. These 3 form 1 bundle, the posterior palatine nerve and its arteriole another.

The anterior bundle enters the posterior palatine canal lying between the internal surface of the superior maxillary and the vertical plate of the palate bone. The posterior palatine nerve and its accompanying artery diverge from the anterior bundle at an acute angle. Directed downward and backward, it enters a canal grooved in the thickness of the vertical plate of the palate bone. This canal, traversing spongy bone, emerges at the lower surface of the pyramidal palatine process, in front of the base of the pterygoid process and on the prolongation of the posterior border of the horizontal plate of the palate bone. In the upper part of the canal, the posterior palatine nerve divides into 2 branches, the anterior sensory and the posterior motor. The sensory branch, at a variable site, subdivides into 2 terminal branches. One branch enters a small canal in the vertical palatine plate. This canal joins the posterior palatine canal in front at a variable point, usually 1 mm. above the lower opening of the posterior palatine canal. The nerve issues through this opening, passing to the mucosa of the lower aspect of the soft palate, its distribution being limited. The other sensory branch almost constantly issues through an orifice on the lower aspect of the pyramidal process. The motor branch, emerging from the canal, bends backward at a right angle to enter the thickness of the soft palate. It is accompanied by an arteriole,

is not more than 0.5 mm. in diameter and advances on the lower aspect of the palate, covered by the thick, glandular layer, which renders its dissection very difficult. It is directed backward and inward and applied against the lower surface of the aponeurosis of the palate a little inside the pterygoid process. Here its usual course is 2 to 3 mm. long, the limits being 1 to 10 mm. It forms an internal and an external branch, which continue the original direction. Both nearly parallel branches are applied to the lower surface of the palatoglossus, which advances on the lower surface of the aponeurosis. Each branch divides into 2 terminal fibers. Of those from the external branch, 1 usually supplies the palatoglossus, approaching its lower surface; the other supplies the palatine head of the palatopharyngeus, which it enters below, behind the palatoglossus not far from the median line.

The terminal fibers of the internal branch vary. One usually supplies the levator veli palati, the other the azygos uvulae. The latter branch perforates the palatine bundle of the palatopharyngeus and sometimes the palatoglossus, to enter the posterior fourth of the lateral border of the azygos, or sometimes its dorsal surface near the lateral border. The fibers going to the levator veli palati perforate the palatine bundle of the palatopharyngeus, entering the lower surface of the levator behind the velar aponeurosis. Sometimes the nerve does not perforate the palatopharyngeus but turns to ascend, passing behind the palatoglossus and slightly forward between the palatoglossus and palatopharyngeus, entering the levator by doubling the anterior border of the palatine bundle of the palatopharyngeus. The course of the motor fibers varies. In 1 case the nerve divided into an external, a middle and an internal, branch. The first 2 branches supplied the azygos uvulae and the palatoglossus, the internal branch supplying the levator veli palati and the palatopharyngeus. In another case, 2 branches were formed, the external supplying the palatoglossus and the azygos, the internal supplying the palatopharyngeus and the levator. The azygos may receive 2 fibers, of which 1, accessory, is derived from the nerve supplying the levator. In 1 case the nerve of the palatoglossus was very long. In a specially interesting case, a small muscular bundle emerged from the posterior palatine canal, forming 2 branches, of which 1 advanced to the levator veli, the other to the palatopharyngeus. Here the posterior palatine nerve supplied only the palatoglossus and the azygos.

From the upper part of the pharyngeal plexus, on the external aspect of the superior constrictor, and behind the stylopharyngeus, emerges a fiber passing between the superior and middle constrictors and ending in the vertical fibers of the palatopharyngeus. The author has never been able to trace the nerve of the stylopharyngeus into the palatopharyngeus (Luschka's report), nor has he found the small fiber from the glossopharyngeus, and the so-called pharyngobasilar branch, described by Krause.

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(1a—243)

(1a—243)

#### **Anastomosis between the Glossopharyngeal and Hypoglossal Nerves.**

*A. Froes da Fonseca, Anat. Anz., Jena, 55: 551, Aug. 10, 1922.*

In an adult negro was found a branch of the hypoglossal nerve, starting 3 cm. beyond its emergence from the anterior condyloid fora-

men, coursing to the posterior branch of the glossopharyngeal nerve. Though junction of the fibers of the ninth and twelfth cranial nerves is not uncommon in man and animals, the author found no reference in the literature regarding the transition of fibers from the one nerve into the other. In the present case, however, a branch of the glossopharyngeal nerve which originated behind the aforesaid anastomosis contained fibers of both nerves and reentered the hypoglossal nerve after coursing 4 cm. The author assumes that a group of fibers originating in the nucleus of the twelfth nerve were already united with fibers of the ninth nerve in the medulla and after an initial course in the glossopharyngeal nerve again united with the hypoglossal nerve.

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(1a—244)

(1a—244)

**A New Form of a Tensor Muscle (Tensor Arcus Cruralis) of Poupart's Ligament.**

*R. Patry and W. Muller, Bull. et mém. Soc. anat. de Paris, 92: 279, May-June, 1922.*

The authors describe a musculo-aponeurotic fasciculus parallel to Poupart's ligament on both sides and lying between the internal oblique and the aponeurosis of the external oblique. On the left side, the fasciculus was attached externally to Poupart's ligament by a tendinous sheet adherent to the lower fibers of the internal oblique but separated from the aponeurosis of the external oblique by loose cellular tissue. The internal insertion was by 3 heads: The upper head, 4 cm. wide, passed in front of the rectus and was lost between the aponeuroses of the external and internal oblique; the middle head, 1.5 cm. wide, was similarly inserted, passing in front of the pyramidalis; the lower head, 1 cm. wide, was attached to the spine of the pubis in front of the conjoined tendon. On the right side, muscular bundles were attached to Poupart's ligament by 2 tendinous roots to the external and middle parts of the ligament. The tendinous sheet covered the entrance of the round ligament into the inguinal canal, as on the left side. One of the muscular bundles was lost in the internal fibers of the internal oblique, the other passed between the aponeuroses of the external and internal oblique, terminating in front of the rectus and pyramidalis.

The structure, tendinous outside, muscular inside, united with the lower border of the transversalis and internal oblique to form the roof of the inguinal canal. The genital branch of the iliohypogastric nerve crossed the middle of the bundles. Abdominal fibers of this nerve supplied the muscular tissue. The structure thus described differs from that described by Grüber, Knott and Auvray, in the lack of insertion into the rectus and the external situation of the tendinous portion present in the authors' specimen.

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(1a—245)

(1a—245)

**The Narrow Gastric Cells.**

*F. Ramond and A. Kirchberg, Bull. et mém. Soc. anat. de Paris, 92: 229, May-June, 1922.*

The authors describe a long, narrow cell lying between, and compressed by the ordinary cells of the gastric epithelium. A slender,



pointed tip lies near the basal membrane. The cell-body is thin and dense, staining bright pink with eosin, and deep blue with the Romanowsky stain, which it takes best. Silver nitrate stains it dark brown. The long, narrow nucleus also stains deeply. Above, the protoplasm forms a cup holding mucus staining like ordinary gastric mucus. The mucous cup thins out at the free surface of the epithelium. Normally, the cells described are rare in the superficial human gastric epithelium, somewhat more numerous at the level of the necks of the gastric glands and very rare at the level of the fundi of the peptic and pyloric glands. They are increased in chronic gastritis, whether it be simple or the form accompanying cancer or ulcer. They were very numerous in a case of chronic, atrophic gastritis. In a case of cancer, with metastases, they were found in secondary islands of tumor tissue present in the liver and glands. Inflammation increases their size, their form and staining remaining unaltered. At the level of the fundi of the gastric glands, they become shorter and thicker and their mucous cups larger. It has not been conclusively shown that inflammation increases the number of these cells. The latter are probably more numerous normally than one might suppose, since they are so flattened out that they may be easily mistaken for intercellular cement.

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(1a-246)

(1a-246)

**Anatomy of the Capillaries.**

*Vimtrup, Klin. Wchnschr., Berlin, 1:1696, Aug. 19, 1922.*

The question of the mechanism of contraction of the capillaries is again to the fore. There are 2 different theories about it. The author examined living larvae of Triton and Rana, and the webs and nictitating membranes of Rana, and found that the contraction of the capillaries is to be attributed primarily to a contraction of the cells outside the endothelial wall. He proposes naming these cells Rouget's cells, from their discoverer.

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(1a-247)

(1a-247)

**Mixed Cultures of Pure Strains of Fibroblasts and Epithelial Cells.**

*Ebeling and Albert Fischer, J. Exper. Med., 36:285,*

the question of dedifferentiation or transformation of an indifferent embryonic cell type, when cultivated in under discussion. In order to settle this question, it interest to determine whether epithelial cells and fibro-distinguished from one another after they had been v side by side in the same culture for several genera-

of a 2 month old strain of epithelium and a 10 year broblasts were cultivated together for several genera-  
bined culture showed a peripheral growth composed of  
the only apparent indication of the presence of epi-

thelium was that the central portion of the culture appeared semi-transparent and homogeneous. At this stage the mixed cultures were subdivided and subcultures made. These in turn were allowed to grow for 48 hours, and were again subdivided through the central portion. This procedure was continued for 7 generations and then the preparations were fixed, sectioned, and stained by Van Gieson's method. The differential Van Gieson stain brings out the chemical difference between the 2 cell types when they are allowed to grow together. With this stain the cultures showed the epithelium stained greenish yellow and the fibroblasts and their fibrillae pink. Epithelium and fibroblasts cultivated in vitro remain 2 different types of cells, and maintain their individual characteristics. Under the conditions of the experiments, no dedifferentiation takes place.

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(1a—248)

(1a—248)

**The Technic of Tissue Cultures of Earthworms in Vitro.**

*A. Krontowsky and R. Rumianzew, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:291, July 21, 1922.*

All lumbricoides are capable of easily regenerating the posterior and anterior ends of their bodies. When the regeneration bud develops, the tissues lose their differentiation and from this rejuvenated tissue varied organs are developed. The culture medium used in these experiments was agar mixed with tissue extracts; the latter furnished the nutrient material, while the agar supplied the mechanical substrate. Sterilization of the tissue extract was best effected by filtration through a Chamberland filter. Through special precautions, the portions of the worm body were obtained free from bacteria. It was possible to obtain cultures of regeneration tissue 5-6 days old; tissues of the regeneration bud of the posterior segment of immature individuals, dissèpiments and blood-vessels with chloragogenous tissue. In 12-24 hours after plating, a small zone of growth could be seen. This growing zone, which later increased in size, was composed of cells varying in size and form, being rounded, spindle-shaped and wedge-shaped. Structurally, they showed a general resemblance to mesenchymatous embryonic tissue. Some of the preparations were fixed in toto, after the method of Camoy and Helly, and stained with Böhmer's hematoxylin. At times, large cells with large nuclei and well staining nucleolus were found along with similar cells having a round nucleus, small nucleolus and small chromatin particles; the large cells were usually arranged in groups in the vicinity of the portion of body. Division seemed to be amitotic; karyokinetic figures were never encountered, while frequently pictures were obtained which closely resembled the various amitotic stages. In cultures of Anodonta, an emigration of leukocytes, but no growth, was observed.

In view of the increase in the number of cells and their active proliferation into the surrounding culture medium, the process may be regarded as a true tissue culture. Since these cultures differ in growth from other cultures, e. g. from the so-called connective tissue type, it may be possible that the growth varies for each class of invertebrates.

ABNORMITIES

(1a—249)

(1a—249)

**A Case of Abnormal Course of the Pulmonary Artery.**

*R. Lund and W. Munck, Virchow's Arch. f. path. Anat., Berlin, 238:153, June 14, 1922.*

While abnormalities in the course of the pulmonary artery ordinarily have only an anatomic interest, such an anomaly in the author's case was of clinical importance. During all of its 5 months of life, a child had had signs of tracheal stenosis which at last grew acutely worse; an attempt at tracheotomy was unsuccessful as the cannula could not be introduced. On autopsy the findings were as follows: (1) The left branch of the pulmonary artery originated at an abnormal place, so that Botallo's duct lay centrally from it instead of peripherally. (2) The left branch of the pulmonary artery ran behind the trachea. (3) The trachea was contracted in a funnel shape, most so at the place where the branch of the left pulmonary artery passed around it. Evidently the tracheal stenosis was a result of the anomaly of the artery. The fatal acute exacerbation of the stenosis was caused by a slight inflammation of the tracheal mucous membrane (without a membrane) which was found bacteriologically to be a diphtheria. The vessel anomaly is most simply explained by assuming that the left branch of the pulmonary artery originated not from the sixth left aortic arch as is normal, but together with the right branch from the sixth right arch. A second plausible explanation would be the origin of the left branch from the fifth left arch; the lower part of the trachea normally lies in front of this; this would also explain the position of Botallo's duct centrally from the left branch of the pulmonary. The fifth pair of arches disappear very early; some investigators even deny their existence.

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(1a—250)

(1a—250)

**A Costal Anomaly.**

*Merz, Bull. et mém. Soc. anat. de Paris, 92:210, May-June, 1922.*

The condition described was found at autopsy. A process was present 1 cm. from the posterior extremity of the seventh left rib projecting downward and forward from its anterior surface and lower border, to meet a process projecting from the eighth rib. The 2 processes articulated by an amphiarthrosis, the articulating surfaces being united by bundles of fibrous tissue permitting some movement. The upper process was larger than and partly concealed the lower. With the lateral aspect of the vertebral body, the 2 united processes formed an oval foramen, whose longer axis was oblique below and outward and which admitted the intercostal vessels. The structure is analogous with that occurring in crocodiles, although here the "processus uncinatus," so called, is outside, and not inside the thoracic cavity. The condition described is considered a persistence, in man, of the uncinate process of reptiles.

GENERAL PHYSIOLOGY

(1a—251)

(1a—251)

**Elasticity and Internal Pressure of the Tissues.**

*Martin Gildemeister and Luise Hoffmann, Pflüger's Arch. f. d. ges. Physiol., Berlin, June 19, 1922.*

The opposition offered by an organ, as e. g. the human arm to the pressure of a finger, should not be described as hardness but as elasticity, more particularly as pressure elasticity, which may also be called resistance. The present experiments were undertaken in order to investigate the resistance of the integument of the body—cutaneous and subcutaneous tissues—and to draw conclusions concerning the pressure of the fluids permeating the tissues. The measurements were carried out after Gildemeister's momentaneous method. It was found that the elastic resistance of the loose tissues against pressure of short duration is dependent, in the first place, on the hydrostatic pressure of the intracellular fluid and, in the second, on the character, stiffness and tension of the topmost layer. The measurements were taken by means of the "ballistic elastometer," the contact time of a falling hammer being registered electrically; this time is the shorter, the greater the resistance. The resistance of the lower arm changes in correspondence with the changes in the blood circulation. In venous stasis, it soon begins to increase, at first slowly and then more rapidly, returning to normal very quickly after removal of the compression bandage. In anemia (Esmarch's bandage), the opposite changes are observed, but in a much smaller degree. Apparently, the resistance is parallel to the capillary pressure. The cutaneous tension also plays a part; the resistance increases, the farther the elbow is extended. By gauging the elastometer on models (air-filled rubber balls, fresh lungs of cats and rabbits), it was possible to obtain absolute values for the tissue pressure; the lower arm showed about 10 mm. Hg, with a margin of uncertainty amounting to some centimeters upward and downward. According to Bayless-Starling, the hydrostatic pressure of the lymph is equal to the capillary pressure minus the difference between the colloid-osmotic pressure in the blood and in the lymph, which is about 16 mm. Hg. The capillary pressure is not known with certainty, all methods of measurement employed so far being open to grave objections. If it is estimated at 20-30 mm. Hg, the resulting values of tissue pressure are in fair agreement with the experimental findings.

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(1a—252)

(1a—252)

**Human Axillary Glands.**

*Emil Holmgren, Anat. Anz., Jena, 55: 553, Aug. 10, 1922.*

The author shows that the secretory parts of the sweat-glands are divided into at least 2 sections which differ essentially in structure and function. These sections represent a filtering section (sweat secretion) and a special section producing specific substances. In the case of operative material prepared at body temperature it was found that the gland tubules consist of 2 different sections, one having flat glandular cells which secrete an aqueous noncoagulable fluid, while the other section has cells that send out processes toward the lumen, which

processes are finally cast off and by becoming liquescent yield the secretion in the form of a detritus.

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(1a—253)

(1a—253)

**Balanced, Sterilizable Nutritive Solution of Physiologic H-Ion Concentration.**

*A. Fleisch, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:22, July 28, 1922.*

A fluid can only be regarded as a physiologic substitute when it satisfies certain requirements. (1) Its osmotic pressure must be approximately the same as that of the blood serum. (2) It must be a physiologic mixture of the different kinds of ions. (3) Its H-ion concentration must be approximately that of arterial blood. The so-called physiologic salt solution meets only the first of these requirements. Ringer and Tyrode solutions are much better, there being a better composition of the ions, as they contain NaCl, KCl, CaCl<sub>2</sub>, NaHCO<sub>3</sub>, and also MgCl<sub>2</sub> and PO<sub>4</sub>. But the proportion of potassium to calcium and of monovalent to divalent ions does not entirely correspond. Fresh Ringer solution is too acid, Tyrode solution too alkaline, and neither can be sterilized. The new nutritive solution can be sterilized by keeping certain sterilized constituents separate. A concentrated basic solution is prepared of the neutral salts and phosphates. When the nutritive solution is to be used this basic solution is diluted with distilled water and a measured amount of normal soda solution is added. The basic solution contains NaCl, 10.5 gm.; KCl, 0.5 gm.; CaCl<sub>2</sub>, 0.3 gm.; MgCl<sub>2</sub>, 0.1 gm.; H<sub>3</sub>PO<sub>4</sub> (normal), 5 c.c., and H<sub>2</sub>O, 50 c.c. to 58.7 gm. As sodium chlorid is ordinarily impure it is filtered. For use, 50 c.c. of this solution is added to 1 liter water, sterilized and after cooling saturated with oxygen. At 37° C. the solution gives the same reaction as arterial blood. Then 5 c.c. of a previously sterilized normal soda solution is added; with this 4.26 c.c. of the normal phosphoric acid enters into reaction, forming a mixture of primary and secondary sodium phosphate, carbonic acid and sodium bicarbonate. These mixtures, buffer substances, hold the H<sup>+</sup> with great tenacity. The freezing point is lowered by 0.55° to 0.56°, depending on the water content of the sodium chlorid. The osmotic pressure is the same as that of the blood. The phosphate concentration is double that of cattle serum to produce a better stabilization of the reaction. The CO-ion concentration is kept considerably under that of cattle serum in order to prevent the escape of carbonic acid and thus to increase the alkalinity.

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**Ciliary Movement.**

*Friedrich Alverdes, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:245, July 4, 1922.*

If *Paramecium caudatum* be placed under a cover-glass with some pressure, bright droplets appear on its surface. These increase rapidly in size and number, and the cilia which cover the surface of the body are lost. Most of them drop out without the basal grain and lose the power to strike. Any which have retained the basal grain keep this



power for some little time. The cilia upon the droplet carry out automatic to-and-fro movements with their foot-point while striking, thus indicating that the surface of the droplet is still moist. This motion continues until the stored reserve energy of the cilium has been used up. The difference from free cilia is probably this, that the droplet acts as a seal for the wound and prevents the injurious water from reaching the cilium. It is too early to regard the basal grain as the kinetic center. The cilia may unite in bundles and assume a common rhythm. This rhythm is produced in a purely mechanic way by the pressure and suction action developed in the water and by the concussion of the surface of the droplet. Cilia from different individuals may fall into a common rhythm by the coalescence of 2 such hyalin droplets. Thus, concerted action of the cilia is the result of a purely mechanic process.

In the living animal, the impulses derived from the protoplasm are doubtless the most important factor, yet even in them the mechanic element plays a part. The cilia upon the droplet have lost the faculty of thigmotropic reaction (arrest of motion under the stimulus of contact), while those cilia which still remain in connection with the animal cell retain this power, even though the cell be undergoing dissolution. This shows that the reaction is an indirect one, transmitted through the protoplasm.

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#### **Geotropism of Paramecium Aurelia.**

*I. George Schaefer, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:227, July 4, 1922.*

Certain observations seemed to indicate that the negative geotropism of Paramecium could be changed to a positive form. The question then was whether under certain conditions a positive geotropism really existed, or whether these same conditions affected the locomotor ciliary apparatus in such a manner as to render negative geotropism impossible. The tests were carried out in 1918-1919 at the Bonn Physiological Institute. To determine the intensity of ciliary motion in relation to its locomotor effect, the author employed the method of Nagai, who determined the rapidity of galvanotaxic swimming rapidity. The factors producing a transformation, so called, of geotropism were, without exception, paralytic and consisted in a disturbance of the static mechanism, which interfered with the production of the geotropic effect; that is, it was purely apparent, no positive geotropism resulting but a paralysis of the locomotor apparatus. An overcompensation ensues between the absolute strength of the Paramecium and gravity, the latter having the advantage. There is a passive sedimentation that cannot be designated as positive geotropism, and it is, therefore, improper to speak of a transformation of geotropism.

The mechanic nature and the physical basis of geotropic motion are especially well brought out. The physical basis is seen in external friction. The friction resistance is so great that in water the Paramecium body sinks only with a speed of 1 mm. per second. To overcome this friction resistance, the Paramecium requires a power of 0.00096 mg., while its total absolute power is 0.001079 mg. Nearly

90% of this is used to overcome the friction. According to the position of the resting animal, the friction varies at the cilia in different parts of the animal body, and this variation furnishes the stimulus which determines direction. In consequence of this preponderance of purely mechanic factors, it is useless to designate the tests as those of reversal or transformation.

## CIRCULATORY SYSTEM

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### **The Easy Manufacture of Aluminum Threads for the String Galvanometer.**

*A. Weber, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:250, July 4, 1922.*

A method is described for making thin aluminum strings (e. g. 3 microns thick) from the Wollaston wires in the market. By means of Wood's metal, pieces of the aluminum strings 9.3 cm. long are soldered for a distance of 3 mm. to notched brass pins. Of the free end of the wires 1.5-2 mm. is dipped into a thin solution of flexible collodion and the thread is cut off by means of concentrated nitric acid, using a special apparatus (Leitz) which severs the wires in about 4 minutes (by the medium of light from a Lilliput arc lamp and a convex lens). The brass pin which is to receive the free end of the wire is heated until the solder melts, and the string is introduced. The aluminum strings have at least the same resistance as platinum strings, and require a much shorter time exposure, hence they furnish an undistorted electrocardiogram with a much weaker magnetic field. For clinical purposes the small Edelmann electrocardiograph (string galvanometer) will, therefore, presumably suffice in future.

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### **The String Galvanometer. Damping by Condensers.**

*Martin Gildemeister, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:123, June 19, 1922.*

Einthoven found that a string galvanometer with the string swinging periodically can be damped up to the point of being rendered aperiodic by connection with a condenser. The present study, which is of a purely physical character, is concerned with the theory of that process. The author arrives at the conclusion that a registration apparatus in which electromagnetic damping plays a part can be rendered aperiodic for any external resistance by appropriate connection with a condenser, if it is aperiodic or superaperiodic in short circuit. If that is not the case, the complete attainment of the aperiodic state is possible only up to certain conditions of damping in the circuit without condenser. Approximately, it is possible, if  $Db > 1 - 0.2 \sqrt{1 - Da}$ , where  $Da$  represents the relative damping constant of the string swinging closed through the resistance  $Wa$ , and  $Db$  the corresponding constant of the short circuit. The exact conditions may be seen from a graphic representation of the relations between  $Da$  and  $Db$ . The product of frequency, resulting resistance, and capacity, by which the

aperiodic state is achieved, is determined by the 2 parameters: the damping constant without condenser—(1) in short circuit, and (2) in the intended connection. The larger these constants, the smaller the product. The same considerations also meet the case of the moving coil galvanometer. Even though Frank's work has taught us that exactness of registration is affected more adversely by intensive than by insufficient damping, these investigations are of practical significance in registering processes with a period considerably longer than that of the registration apparatus, especially on account of the saving effected with respect to calculations of correction.

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**Electrocardiographic Studies on Small Warm-Blooded Animals.**

*Ernst Oppenheimer, Ztschr. f. d. ges. exper. Med., Berlin, 28:96, June 7, 1922.*

This is a detailed study of electrocardiograms of the larger laboratory animals; registration of the activity of heart is effected with the string galvanometer, and by means of this instrument the influence of various chemical substances on the cardiac activity of dogs, cats, rabbits and guinea-pigs has been frequently observed and registered. No electrocardiographic observations have so far been published concerning the smaller experimental animals (rats, mice). Present-day circumstances compel the abandonment of rabbits and of the more expensive dogs and cats for such experimental work and the use of the much cheaper and more readily procurable smaller mammals, particularly for such study as electrobiologic research.

In place of electrodes the author used very fine pins, stuck under the animal's skin, to one end of which was attached a wire; in its turn the latter was connected to wires leading to the galvanometer strings. In the mouse the pulse rate oscillated between 500 and 700, and in the rat between 360 and 520 beats per minute. In birds (sparrows, finches, etc.), with the electrocardiograph directed downward, the pulse rate oscillated between 400 and 900 beats per minute. Following administration of atropin, there was for the most part a slowing of the pulse; in no case was there an acceleration. Following administration of adrenalin alone there was no tachycardia; but adrenalin given after atropin succeeded in effecting a very slight acceleration of the pulse rate, barely exceeding normal; strophanthin caused a slight slowing of the pulse, particularly after nicotin.

It was easy to assume that the acceleration of pulse rate observed was due to the restraint and more or less forcible detention of the animal, with its resultant irritation, and that the lack of acceleration of pulse rate following administration of drugs usually causing this effect in other experimental animals was due to the fact that the birds' hearts, for instance, under these circumstances, were in abnormal conditions of irritability to begin with and, as a matter of fact, were already yielding their maximum of functional response before the experiment was actually begun. If this assumption were correct, the irritation should have been continuous, since the prone position maintained even for hours at a time and the lack of any perceptible stimulating influence

usually cause no change in the pulse rate of animals. Anesthesia with urethan demonstrated that acceleration of the pulse rate did not depend on unusual stimulation; both before and after anesthesia with urethan, and even during most profound narcosis, the pulse rate of these animals remained the same. The effects of atropin and adrenalin administered to narcotized animals did not differ in the least from those in non-anesthetized animals.

It therefore seems beyond doubt that variations in pulse rate reported so far are not due to faulty technic, but rest on a special property of small warm-blooded animals, especially small birds.

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**Active Diastole.**

*A. K. Siewert, Ztschr. f. d. ges. exper. Med., Berlin, 28:324, June 30, 1922.*

Four dogs were given Mo-curare. The thorax was then opened under artificial respiration. Through the right carotid a sound was introduced and connected with a differential manometer. Strophanthin was injected into the pericardium of 2 dogs, and in 2 others dyspnea was induced by diminishing the air supply. This experiment on intracardiac pressure resulted in increase of systolic pressure (by a maximum of about 71.6%), which was particularly intense with impeded respiration, and in a considerably greater increase of diastolic pressure (up to 212% of the initial level), also more intense with impeded respiration. Further experiments, under the same conditions, were carried out with Hürthle's tonograph or Fuck's manometer. In the latter case an electrocardiogram was also taken. In this experimental procedure, the curves also showed distinct negative pressure after injections of strophanthin and production of dyspnea. The curves demonstrate that diastole consists of 2 parts. In the first part the pressure is diminished in the form of a parabolic curve which corresponds to relaxation of the muscle after systole; in the second part the pressure diminishes further and may attain a very considerable negative level (in dyspnea after strophanthin), which corresponds to active diastole. Comparison of this part of the curve (*D*) with the electrocardiogram shows that it appears simultaneously with the contraction of the auricles, at times a little later and at times considerably earlier. This active part of diastole is divided (up to 260%) in the initial stage of the strophanthin action (after pericardial injections). With further poisoning by cardiac drugs the active part of diastole is absent, the period of relaxation becomes shorter and the aspirating activity of diastole may be entirely abolished.

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**Movements of the Heart.**

*Ernst Simonsohn, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:410, July 21, 1922.*

The first tests were carried out by gluing small paper flags, 12-13 mm. in length and weighing only a few milligrams, to circular disks of thin cardboard measuring 2-3 sq. mm. in area. These disks were then placed upon diverse regions of the exposed heart. The

excursions of the tips of these flags in the longitudinal and the transverse axes of the heart were read off from a scale of millimeter paper placed behind them. But the alterations of the dimensions of depth, i. e. the state of cardiac convexity, produce complicated motions which cannot be simply read off. However, even in these tests a triple rhythm of ventricular motion could be determined. The movement of the heart is divided into presystole, i. e. the time of auricular systole; systole; and diastole, i. e. the time during which the ventricle has been emptied of blood (save the residual blood). Nine different regions of the heart were selected for study. The movements in these areas vary in direction and speed, but all the paper strips describe triangular figures. Later these points were marked with tiny bits of paper and their excursions in a longitudinal and transverse direction, magnified 30 times, were measured by means of a micrometer scale. No registration of the changes of depth were made.

The systolic movements of the frog heart radiated to a point of convergence; the base exhibited strong caudal displacements. Those of the center were in the same direction, but less marked, while the apex and points near it moved in the opposite direction, most strongly at the apex. The motion was always to the left. While the animal was being bled to death, the presystolic arching disappeared a few moments after the aorta had been divided. Thus the triple ventricular rhythm was converted into a double. The systolic movement became less; at first it remained regular, then the systolic elevation of the apex disappeared; and afterward the (immobile) point of convergence and with it the rotation which may have existed. Previous to its disappearance, the point of convergence was displaced toward the right base. Overdistention of the blood-vessels from the injection of physiologic salt solution into the vein of the abdominal wall, produced the following: If a line, rather than points, of convergence had existed at the start, 0.2 c.c. salt solution brought out the point clearly and distinctly. Injections of 1.5 c.c. produced a threefold increase in the volume of the heart, and a raising of the organ in toto. The triple rhythm of the ventricular movement disappeared either because in consequence of the high venous pressure, systole and presystole alternated directly, or because even in diastole no more blood could be forced into the ventricle. The contraction movements were considerably increased, but otherwise normal.

Analogous conditions were found in the rabbit heart, except that, corresponding to the division into 2 ventricles, there existed 2 points of convergence. The total displacement of the ventricle toward the base after loss of blood can be explained by the fact that, with a normal volume of blood, the portions of the heart lying to the cephalic side of the auriculoventricular boundary (aorta and atrium) offer resistance to that portion of cardiac force which acts toward the base.

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#### **A New Method for Measuring the Pressure in the Pulmonary Artery.**

*Walker E. Swift, Gilbert E. Haggart and Cecil K. Drinker, J. Exper. Med., 36:329, Sept. 1, 1922.*

The cannula adopted for this method combines the ideas of Henriques and Schafer. It has 2 parts, a barrel and a stilet. Side tubes



enter the barrel, 1 leading to the pressure recording device and 2 leading to an ordinary washout system. The stilet is well covered with stop-cock grease and makes joints capable of holding water under a pressure of 100 mm. Hg both at the tip and at the knurled head. To insert the cannula one simply grasps the precardial tissue on both sides of the pulmonary artery with hemostats and pushes the cannula through the wall of the artery just as a needle is inserted into a vein. The cannula is held in place by a special clamp on a ring-stand, and tubes are connected with the manometer and washout systems. The cannula is then filled with the anticlot solution employed, and the pulmonary arterial pressure may then be recorded. In order to connect with the blood stream the operator opens the tube leading to the washout system and withdraws the stilet until the light spring upon the side of the barrel engages the groove in the stilet. The tube to the washout system is then closed, and on opening tube to the pressure recording system a tracing is at once obtained. When a suitable length of record has been obtained the tube leading to the washout system is opened and the stilet thrust back into its original position. The cannula can at once be cleansed from the washout system and another tracing made. The same series of maneuvers can be repeated as many times as is required. Descriptive diagrams are helpful in following the method.

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**The Contractility of the Capillaries.**

*R. H. Kahn, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:368, July 21, 1922.*

Kahn undertakes a polemic against the chapter on the "So-Called Contractility of the Capillaries," by R. Klemensiewicz, in Abderhalden's "Handbuch der biologischen Arbeitsmethoden," which attacks with insufficient arguments the work of Steinach and Kahn in which the contractility of capillaries was established.

Indeed, the facts cited by Klemensiewicz agree with the experiences of Steinach and Kahn, and with the later observations of Kukulka. Yet here and there a genuine contractility of the capillaries can be observed, which is connected with the discontinuous arrangement of the contractile elements. These actual determinations were not considered by Klemensiewicz.

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**The Circulation in the Mammalian Bone-Marrow. With Especial Reference to the Factors Concerned in the Movement of Red Blood-Cells from the Bone-Marrow into the Circulating Blood, as Disclosed by Perfusion of the Tibia of the Dog and by Injections of the Bone-Marrow in the Rabbit and Cat.**

*Cecil K. Drinker, Katherine R. Drinker and Charles C. Lund, Am. J. Physiol., 62:1, Sept. 1, 1922.*

Having isolated the tibia of the dog for perfusion, it was next essential to determine the pressure conditions in the isolated tibia as circulated by the animal, and also to measure the rate of normal blood flow in the preparation. The authors employed a rather intricate perfusion pump (illustrated and described in the article). In the per-

fusion and injection experiments morphin sulphate and urethan were the anesthetics used in dogs, while urethan alone was employed for cats and rabbits. In every case it was desired to obtain correlation between the condition of the bone-marrow and the cellular content of the circulating blood, with particular reference to the manner in which adult red cells reach the circulation.

By the use of methods of perfusion and of injection, so arranged as to approach the physiologic limits set by the animal under experiment, the authors observed that the capillaries conducting blood in the bone-marrow of the mammal in a condition of normal blood formation are closed structures, lined throughout with endothelium, and not in communication with the marrow parenchyma. Under conditions of active red blood-cell formation, the extremely delicate walls of these capillaries are grown through by irregularly placed red cells in varying stages of maturity. The capillaries are thus, for a period of varying length, open structures, but the opening presented does not result in flooding the marrow parenchyma with blood because of the packing of the immature blood-cells, which is an essential phase in the process of encroachment upon the capillary wall. The normal mature erythrocytes are delivered to the blood-stream through the extraordinarily thin endothelial membrane lining the capillaries. This process must occur constantly, the authors believe, and under the influence of such slight difference in pressure between the outside and inside of the blood-vessels as to cause no actual vascular rupture. The stimulus causing growth of red blood-forming tissue is responsible also for delivery of these cells to the circulation.

## DIGESTIVE SYSTEM

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**Cholin as the Hormone of Intestinal Peristalsis. VII. Cholin Content of the Gastro-Intestinal Tract during Fasting and after the Administration of Morphin.**

*K. Arai, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:390, July 21, 1922.*

Exceptionally constant values are obtained in cats when a one-hour dialysis is used to determine the cholin content of the stomach and the small intestine. Contrary to some opinions expressed in literature, the amount of cholin in the stomach and small intestine of the cat after 17, 48 and 90 hours of fasting was the same as immediately after feeding. In dogs, the amount of cholin in stomach and small intestine was distinctly diminished for 24 hours after the injection of 6 mg. morphin per kilogram of body weight. This bears out the statement made by Zuntz and György. However, isolated portions of the intestine of dogs, normal and morphinized, showed the same sensitiveness to the dialysate from the stomach and the small intestine of normal as of morphinized dogs, contrary to the statement of these 2 authors. The cholin content of stomach and small intestine in cats is unaffected by a colocynth diarrhea. If this diarrhea is relieved by proper doses of morphin, leading to a complete cessation of peristalsis, no change occurs in the amount of cholin in the small intestine, while that of the stomach is somewhat diminished, in accordance with earlier findings. Therefore

it cannot be assumed that the constipating action of morphin depends upon a loss of cholin from stomach and small intestine. Summarizing the facts thus far determined concerning the cholin content of the gastro-intestinal tract under diverse conditions, we arrive at the following conclusions:

The amount of cholin is normal in chloroform paralysis, laparotomy, iodine peritonitis, during starvation, diarrhea due to colocynth, and after morphin injections of 1 mg. per kilogram of body weight. When the morphin dose is increased to 6 mg. per kilogram of body weight, the amount of cholin found in the stomach is diminished, while that of the small intestine remains normal. Doses of 20 mg. per kilogram of body weight reduce the amount in both stomach and intestine. When morphin in doses of 6 mg. per kilogram of body weight is given to offset the colocynth purge, the stomach shows a reduced, the small intestine a normal cholin content.

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### **Biliary Secretion. II.**

*Ernst Neubauer, Biochem. Ztschr., Berlin, 130: 556, July 20, 1922.*

Conflicting properties have been attributed to various substances, some being held to promote and others to limit the secretion of bile. Only bile and bile acid salts are decided cholagogues. It was safest, therefore, to carry out experiments only with bile and sodium cholate and glycocholate. The experimental results show that the amount of bile is increased by bile, sodium salts of cholic acid and of glycocholic and taurocholic acid, ethyl cholate, and Mylins' iodine compound with cholic acid and its nearest oxidation product, dehydrocholic acid. It is noteworthy that no cholagogue action pertains to the decomposition products of cholic acid, cholanic (carboxyl) acid and cholatrienic (carboxyl) acid, nor to the oxidation products, bilianic and cilianic acids. The strongest cholagogue action is produced by desoxycholic acid, a normal constituent of bile and closely related chemically to cholic acid. The cholagogue action of intravenously injected bile and bile acid salts begins in a few seconds. The bile secretion curve rises steeply, attains its greatest height in 1-2 minutes after sodium cholate and its paired products, in the second minute after sodium desoxycholate, and then falls slowly. Cholagogue bile acids increase biliary secretion pressure when injected intravenously. Autobile injection had no influence on surface tension, specific weight and percentage of dry residue. Following injection of sodium cholate, glycocholate and taurocholate the surface tension of the bile increased and approached that of water, while specific weight and absolute as well as relative dry residue were likewise augmented. Desoxycholic acid either left all 3 conditions unaffected or it increased specific weight and dry residue with simultaneous diminution of surface tension. The surface tension of bile decreases with increasing concentration of bile acid. Under the influence of sodium cholate, glycocholate and taurocholate surface tension increased although the bile acid content rose simultaneously. This might be conditioned on diminution of the sodium chlorid concentration of the bile. Also, bile acids may form colloidal complexes with certain substances, or may enter into additive combinations, in accordance

with the choleic acid principle discovered by Wieland and Sorge; the surface tension of these combinations differs from that of bile acid salts as such. The most probable assumption is that the paradoxical increase of surface tension depends on addition to the bile acid of a substance occurring possibly only in traces or on a substance present in greater than normal amount. The same effect may also be obtained by injection into a mesenteric vein, while a similar effect may be expected from direct administration into the stomach or duodenum. In the case of sodium desoxycholate only the intense coloration of the bile is absent and the urine contains no hemoglobin as frequently happens after intravenous administration. Normal bile secretion is independent in the widest sense of the nervous system and this applies also to biliary flooding produced by bile acid salts. On the other hand, the volume of circulation is of essential importance to the secretory activity of the glands.

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### **Study of the Formation of Bile-Pigment.**

*F. Rosenthal and E. Melchior, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:28, July 28, 1922.*

Formerly, based on the experiments of Minkowski and Naunyn, it was taught that every form of icterus originated in the liver; but now it is recognized that the formation of bile pigment outside the liver plays a decisive part in the pathogenesis of icterus. This takes place in the reticulo-endothelial apparatus for metabolism, according to Aschoff-Landau. The nonappearance of arseniureted hydrogen icterus in birds who have had their livers removed is attributed to the simultaneous removal of Kupffer's cells. As bile pigment cannot be demonstrated in Kupffer's cells under normal conditions, McNee conceives that their physiologic function is to split off and store the iron-containing constituent of hemoglobin after taking up the erythrocytes, while they cast aside the iron-free, pigment-containing part. After intoxication, there is great increase of Kupffer's cells and they are cast off into the blood, where they are found in the liver veins, in the blood of the right heart and in the lung capillaries. In them are numerous erythrocytes with yellow and green pigments like hemosiderin granules. The latter are also free in the blood. This indicates destruction of Kupffer's stellate cells causing a hematogenous icterus without involvement of the liver parenchyma. Minkowski and Naunyn often found in the spleen and bone-marrow enough cells containing blood-corpuscles, after  $AsH_3$  intoxication, to have made abundant bile pigment formation possible after extirpation of the liver if it had been formed there. But the phenomenon did not occur.

Lepehne proceeded from Cohn's demonstration that the stellate cells of the rabbit's liver store silver immediately after the intravenous injection of collargol. As a result of the supposed paralysis of the reticulo-endothelial apparatus resulting from this, the formation of bile pigment could be inhibited. Others also found that the blocking of this cellular system, even with iron, as Eppinger did experimentally, prevented the appearance of icterus. His own experiment made on doves showed the rapid storing of collargol in the stellate cells. This blockade lasted for at least 48 hours; but no noteworthy limitation of bile

pigment could be demonstrated. Then mechanic interference was substituted and the bile-ducts ligated. Although before there had been pure biliverdin bile in these, afterward there was no biliverdin in the blood, but bilirubin. Also when the doves lived longer, an intense blood icterus could not be produced. The mechanic icterus in doves was green in the urine and tissues, while the simultaneous blood icterus was yellow, that is bilirubinemia, not biliverdinemia. From what precedes, it is evident that collargol injection and filling of the stellate cells with silver causes a functional paralysis of the reticulo-endothelial cells and the icterus caused by ligation is stopped or at least greatly weakened. The experiments showed that in spite of maximum collargol blockade of the Kupffer cells, the production of bile pigment still goes on. It is, therefore, not proved that the stellate cells of the liver are the chief place for the formation of bile pigment.

## METABOLISM

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**The Performance and Calculation of Metabolism Experiments with Ruminants.**

*A. C. Andersen, Biochem. Ztschr., Berlin, 130: 143, June 20, 1922.*

The heat production of an animal on a given fodder may be calculated from the respiratory gaseous exchange if the requisite experimental data are available. A knowledge of carbon dioxid production, oxygen consumption and amounts of nitrogen excreted in the urine suffice for the purposes of the calculation. The amount of nitrogen yields the amount of oxidized albumin and from the latter the amount of oxygen utilized and the amount of carbon dioxid are obtained. The remainder of the evolved carbon dioxid and of the consumed oxygen is derived from the oxidation of the nonnitrogenous constituents of the fodder. The proportion of these two values therefore represents the respiratory quotient of these constituents, from which the heat production of the metabolized nonnitrogenous portions of the fodder may be easily calculated by means of a table constructed by Zuntz showing the caloric value of oxygen with different respiratory quotients. The additional heat produced by albumin oxidation then yields the total heat production. But in the case of animals with strong fermentation in the digestive tract, especially ruminants, the conditions are not so simple. In fermentation, carbon dioxid and methane are formed, and the direct determination of heat production by the aforesaid method then leads to erroneous results because a part of the evolved carbon dioxid is derived not from actual combustion in the animal body, but from fermentation. In order to render possible the calculation of heat production in such animals Zuntz and his coworkers effected the determination of the true respiratory gaseous exchange by separating the gases from pulmonary respiration and those derived from the digestive tract with the aid of a tracheal cannula. They assumed that the other method of calculation is applicable only if the amount of carbon dioxid discharging through the cannula and not the total amount elaborated is reckoned with. In the case of isolated laboratory experiments such an experimental procedure can be carried out without special difficulties. Not so in large series with many animals. No actual proof is furnished that the amount of carbon dioxid discharged through the cannula corresponds exactly to that formed during combustion in the organism and



such proof is probably unobtainable inasmuch as methane as well as carbon dioxide are resorbed from the digestive tract and the resorbed gases are subsequently eliminated by the lungs. As regards methane, experiments conducted by Klein in Zuntz's laboratory have shown that about one-third of the total methane formed is resorbed and expired through the lung. Unpublished experiments yielded approximately the same result. Probably it is hardly possible to determine the amount of carbon dioxide formed in the digestive apparatus and resorbed and expired by the lungs. Moreover, it is compensated partly by possible cutaneous respiration and partly by the following behavior. A considerable amount of the total carbon dioxide formed is not produced directly by fermentation but in consequence of the formation of acids during fermentation; these acids are neutralized by salivary carbonates with evolution of carbon dioxide. If the acids were resorbed as such their entire carbon would appear in the form of carbon dioxide from the lungs if combustion is complete. But as they are neutralized in the first stomach or in the oral cavity during rumination, i. e. outside the organism, and are then resorbed in the form of salts, a part of their carbon is retained as carbonate in the blood. It is obvious therefore that the amount of carbon dioxide expired through the lungs under these conditions is less than that actually corresponding to combustion if no compensation by resorption of carbon dioxide from the digestive tract takes place. Proof that these sources of error compensate each other under all conditions is of course hardly possible. Zuntz's table of the caloric value of oxygen with different respiratory quotients is constructed on the assumption that the nonnitrogenous substances oxidized in the organism are either fats or carbohydrates. Whether the numerical values of this table can be properly employed if the oxidized substances were fermentative products with other respiratory quotients and other oxidation values than those on which the table is based, must be considered questionable. Zuntz himself called attention to this and he and his coworkers carried out experiments to elucidate the question. From these they believe it possible to employ the table even in such a case without causing considerable errors. Even if this be so there is still some uncertainty, as in the determination of the respiratory quotients. A method of calculation leading to the same goal without these sources of error would therefore prove useful. Such a method is now communicated. This renders possible the calculation of heat production in metabolic experiments with ruminants from the amount of urinary nitrogen, oxygen consumption, total amount of carbon dioxide formed and of the amount of methane formed during fermentation. On the other hand a separation of the gases formed by fermentation in the digestive tract and those produced by combustion in the organism is not requisite and it is therefore unnecessary to perform tracheotomy. The method of calculation shows that it is possible to determine an animal's heat production accurately even when the respiratory quotient exceeds 1 owing to the formation of fat in the organism.

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**A Self-Feeder for Rats.**

*Ralph Hoagland, J. Lab. & Clin. Med., 7:687, Aug., 1922.*

Hoagland has devised a self-feeding apparatus for quantitative feeding tests with rats, that will allow rats free access to the feed and

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yet will prevent their wasting it or contaminating it with excrement. It consists of 3 separate parts: the receptacle for waste feed, also serving as base for feeder, the vestibule and feed hopper and cover to feed hopper. The feeder is made of heavy-coated bright tin and galvanized wire screen,  $\frac{1}{8}$  in. mesh. The respective parts of all feeders are interchangeable. The feed hopper will hold approximately 100 gm. of feed, depending upon its character. The feed hopper is filled with feed and then weighed. At the end of a week the feeder is freed from any adhering feces and weighed. The loss in weight represents the feed consumed, provided there has been no wastage. The screen floor to the vestibule catches the feces so that they do not contaminate any feed which may have fallen into the base of the feeder. After several months' experience with this self-feeder 2 slight modifications are suggested: (1) increase in the depth of the waste-feed receptacle from  $1\frac{1}{8}$ - $1\frac{1}{2}$  in., so as to provide more storage room for waste feed; (2) modification of the baffle plate so that it can be raised or lowered as desired to prevent rats from pulling feed out into the vestibule.

A scale drawing of the feeder is reproduced.

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### **The Transformation of Protein into Fat and Fat into Carbohydrate in the Body.**

*Harry Victor Atkinson, J. Metab. Research, 1: 565, May, 1922.*

This paper deals with the disputed transformation of food proteins into tissue fats and of food fats into tissue carbohydrates. The historical facts are reviewed, and feeding experiments, fatty infiltration and degeneration, formation of fat in phosphorus poisoning, formation of adipocere and formation of fat from proteins by lower forms of life are discussed at length. The transformation of food proteins into tissue fats was studied by experiments in which respiratory exchange and heat production of dogs stuffed with large quantities of lean beef heart were measured with a respiration calorimeter and by extensive investigations of chemical blood changes under such conditions. The chemical pathway of the conversion of protein into fat was subjected to critical study and graphic representation. Transformation of food fats into tissue carbohydrates was investigated, with reference to the known reduction of oxidative processes in hibernating animals and under the influence of morphin. The investigations embraced blood changes under the influence of morphin alone, during ingestion of large amounts of fat (olive oil) alone and during ingestion of large amounts of fat while under the influence of morphin (1 gr. morphin sulphate subcutaneously in divided doses). The results of these and of the aforesaid experiments are discussed in detail and tabulated. An extensive bibliography is appended. The following conclusions are reached: (1) When the body's glycogen reservoirs are low, ingestion of large quantities of meat results in deposition of glycogen. (2) Continued ingestion of much meat leads to retention of a pabulum consisting partly of glycogen and partly of fat. Only with great excess of meat is fat alone retained. (3) Morphin depresses oxidative processes in the body, and (4) fat is transformed into sugar under these conditions. (5) Blood sugar is increased when fat alone

is fed to a dog in large quantities, and (6) the increase in sugar under these conditions supports the view that fat can be transformed into sugar.

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**The Products of Protracted Typical Digestion of Casein.**

*S. Fränkel and P. Jellinek, Biochem. Ztschr., Berlin, 130:592, July 20, 1922.*

During digestion of protein by trypsin, it was found that the reaction of free tryptophan with bromin water disappears in the course of very prolonged digestion. This reaction appears only in the course of digestion as soon as free tryptophan has been cleaved from the albumin complex. The maximum is attained in a few days and digestion is then interrupted in order to obtain the largest possible amount of tryptophan. If digestion be continued about 50 days with further additions of trypsin, the reaction of tryptophan with bromin water finally disappears, while the reaction with glyoxylic acid and sulphuric acid, which is also exhibited by combined tryptophan, remains intact. Tryptophan is converted into d-tryptophan anhydrid, which does not give the bromin water reaction; and another aromatic amino-acid, l-tyrosin, is converted under like conditions into d-tyrosin anhydrid. Trypsin, or a ferment accompanying the same (anhydrase), unites 2 molecules (l-tryptophan and l-tyrosin), with their carboxyl groups, under cleavage of 1 molecule water, to form 1 anhydrid. The digestive product, from which only tyrosin and tryptophan had been isolated as anhydrids, had then to be worked up further. Four other substances were isolated, only 3 of which were obtained in sufficient quantities to permit of definite determination. Oxyprolin was prepared by a greatly simplified process.

That free ammonia was formed is of interest because it demonstrates the far-reaching action of the tryptic ferment on protein split-products proceeding from the ammonia, in protracted digestion; in this case on the amins of the amino-dicarboxylic acids. The preparation of methylamin enabled a new function of the pancreatic ferment to be observed, namely, its capacity for splitting off carboxyl groups. The latter substance is histidin anhydrid dihydrochlorid and has not been fully investigated.

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**The Utilization of Urea for the Milk Yield, According to Experiments on Cows.**

*W. Völtz, W. Dietrich and H. Jantzon, Biochem. Ztschr., Berlin, 130:323, July 20, 1922.*

In 4 experiments on 3 cows, 1 kg. urea being employed in each case, 9.53-16.73 kg. milk, or 1188.7-1834.0 gm. solid matter were obtained, corresponding on an average to more than 12.5 kg. milk daily with 1.5 kg. solid matter. Feeding experiments were performed on 3 cows in 3 periods: (1) urea and sugar beet; (2) urea with potato waste, and (3) protein only in the form of earthnut cake. The following comparative values are given: On 1 kg. earthnut cake, 2.14 kg. milk and 287.3 solid matter were produced; on 171 gm. urea and 4.34 kg.

sugar beet, 1.19 kg. milk and 153.7 gm. solid matter, that is, a little more than half that on the first diet. On 1 kg. earthnut cake the yield was 1.63 kg. milk and 189.4 solid matter, but on 177.6 gm. urea with 1.02 kg. potato waste, 1.3 kg. milk and 165.0 solid matter, that is, about 80% of the former yield. The milk yield on earthnut cake had decreased as the cows were in an advanced stage of lactation. That potato waste and urea gave about 20% less milk than earthnut cake probably depends on the ready solubility of urea which enters the intestine without being synthesized to bacterial albumin and therefore naturally becomes valueless. This disadvantage is removed by mixing the urea intimately with the other fodder. The milk constituents were affected, but the fat content was increased only slightly. The amid content rose slightly; this amid can assume the rôle of nutritive albumin to a certain extent. Desire for food was always increased by urea. Urea is also serviceable when small amounts of high grade fodder rich in protein are available, as in winter feeding. Not more than 150 gm. urea (representing 375 gm. digestible raw protein) should be given each day to an animal.

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#### **The Rôle of Bile in Uric Acid Metabolism.**

*Theodor Brugsch and Julius Rother, Klin. Wchnschr., Berlin, 1: 1495, July 22, 1922.*

The exogenous uric acid balance test shows a deficit for which there has thus far been no explanation. The authors have demonstrated the physiologically important fact that the bile is also an agent for uric acid excretion. The true measure of uric acid excretion is the sum of urotropic uric acid excreted with the urine and of enterotropic uric acid excreted with the bile. The quantitative relation of the two has not yet been determined, but the authors suspect that high endogenous uric acid values in icterus are to be attributed to a heterotropia of the liver, the liver giving off biliary uric acid to the blood and to the urine. The low endogenous uric acid values in gout patients are attributed to an opposite form of heterotropia, the enterotropic uric acid values being increased at the expense of the urotropic ones; this is supported by the good effect of cholagogic drugs in gout. The discovery of enterotropic uric acid explains the exogenous uric acid metabolism experiment and the heretofore unexplained finding of uric acid in the feces. The assumption that the liver answers to various stimuli with heterotropia explains the great importance of the liver in purin metabolism. It is possible that the exogenous uric acid has chiefly the character of a stimulating uric acid.

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#### **Respiratory Metabolism in Alimentary Glycemia. I.**

*A. Bernstein and Kurt Holm, Biochem. Ztschr., Berlin, 130: 209, June 20, 1922.*

In order to determine whether the large amount of sugar offered to the organs in toxic glycemia is also subject to increased combustion, experiments were undertaken by numerous blood sugar estimations by Bang's micromethods in addition to continued investigation of gaseous

exchange. In man, the blood sugar rises a few minutes after peroral administration of 100 gm. glucose. Respiratory experiments show that the oxidation of the sugar circulating in the blood does not commence at this time. It sets in  $\frac{1}{2}$ -1 $\frac{1}{2}$  hours later, when the blood sugar has already attained rather high values and frequently when it has reached or exceeded the maximum value. Further oxidation of the sugar may take place with low blood sugar values. Therefore no parallelism exists between the blood sugar level and the extent of sugar oxidation after glucose administration. Experiments in which phosphate was given before glucose did not disclose a distinct influence of phosphate on carbohydrate oxidation. During bodily work, the blood sugar generally rises less after glucose administration and sugar oxidation does not set in sooner. Simultaneous determination of serum sugar, serum fat and respiratory metabolism also showed that after carbohydrate administration the extent of carbohydrate oxidation is not determined by the proportion of serum fat to serum sugar. Increased sugar oxidation commences a few minutes (5-8) after peroral administration of 100 gm. levulose. Blood sugar is increased slightly or not at all. It seems probable that glucose is converted into levulose or into one of the substances closely related to levulose before its oxidation. Blood sugar generally rises less with glucose administration if a carbohydrate meal was given before fasting.

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**The Action of Sugar Concentration on Glycogen Synthesis.**

*Stefan Ederer, Biochem. Ztschr., Berlin, 130:294, June 20, 1922.*

The question of the regulatory mechanism of the constant blood sugar level is attacked from various sides. Pflüger's assumption that regulation is effected by a nervous stimulus was rendered questionable by certain experimental results. When the cerebrum is excluded (Morita), or the spine, the splanchnic nerves, or the nerves coursing to the liver are divided in animals, blood sugar concentration remains unaltered or rapidly attains its normal level. The independence from the sympathetic nervous system was demonstrated by Miculicich's and Pollak's experiments, of disconnecting the sympathetic nervous system by means of ergotoxin from the reacting organ without consequent alterations of the blood sugar value. According to Mansfeld-Blum the liver loses its glycogen in strychnin spasms even when it is disconnected from the central nervous system by division of nerves. In phloridzin diabetes the blood sugar level remains normal even if the sympathetic nervous system is paralyzed by ergotoxin (Pollak). After ergotoxin in amounts that suffice to abolish the action of 1 mg. adrenalin on the blood sugar level, the glycemia values are unchanged. These results also make it appear doubtful that adrenalin acts as a normal hormonal stimulus. They direct attention to blood sugar concentration itself as the means of stimulating the activity of the regulatory apparatus in order to confine the formation and decomposition of glycogen within normal limits. In Pollak's view the nervous system is not an indispensable component of regulation. The question arises how regulation takes place and what action is exercised by sugar concentration directly on the course of glycogen saccharification and storage. The action of



sugar concentration on the glycogen-sugar system was studied experimentally. In vitro, inversion of the reaction course in a synthetic direction could not be demonstrated in the glycogen-glucose reaction system either by increase of glucose or diminution of glycogen concentration, nor by the fixation of glycogen in a form incapable of reaction. From this it may be concluded that blood sugar concentration has no regulatory influence on the blood sugar level, at least not as a function of an active mass in the sense of chemical dynamics.

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**Factors Which Determine the Concentration of Calcium and of Inorganic Phosphorus in the Blood Serum of Rats.**

*Benj. Kramer and John Howland, Bull. Johns Hopkins Hosp., 33: 313, Sept., 1922.*

It is not possible to increase the concentration of calcium and inorganic phosphorus in the blood of rats either by diets or by physical factors, to a point above the normal. A decrease in these salts, however, can be produced by suitable alteration of the diet. The concentration of these salts is not only dependent upon the amount of the salts themselves in the diet, but also upon the amount of vitamins. To secure marked experimental reduction of calcium and phosphorus, the diet must be very low in these substances, and must contain just enough of fish-liver oil or butter-fat to prevent xerophthalmia and to allow moderate growth. If a large allowance of the fat-borne vitamin is given, compensation occurs even on a diet very low in calcium and phosphates, and these salts will appear in normal concentration in the serum. Fish-liver oil is more effective in this way than butter-fat, and vegetable oils are ineffective. With a constant but low oil allowance, the calcium and phosphorus concentration in the blood can be raised to normal (but no further) by increasing calcium and phosphorus in the diet. When the diet is defective in phosphorus and the blood serum therefore also low in inorganic phosphorus, a marked increase in serum phosphorus can be produced by starvation for a few days, by adding phosphorus to the diet, by giving various animal fats, and by exposure to radiation with rays less than 3000 Angstrom units (ultraviolet light). The bearing of these facts upon rickets will be discussed in a later paper.

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**Calcium and Phosphorus Metabolism in Childhood.**

*H. C. Sherman and Edith Hawley, J. Biol. Chem., 53: 375, Aug., 1922.*

This paper describes experiments designed to determine the rate of storage of calcium in normal children of different ages and the nature and amount of the intake required to support optimum calcium storage in the growing child. The complete balance of intake and output of calcium (and in most cases also of phosphorus) was determined by the authors in 4 progressive series of experiments including in all 21 children between the ages of 3 and 14 years and covering a total of 417 experimental days in 139 experiments of 3 days each.

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On an ordinary mixed diet containing daily 750 gm. of milk and furnishing a total of 0.74-1.02 gm. calcium per day, children 3-13 years of age stored 0.15-0.62 gm. calcium per day. The authors found the optimum storage of calcium is made when the diet contains 1 quart of milk per day for each child. In general the conditions influencing the storage of calcium tended to influence that of phosphorus in the same direction.

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**The Metabolism of Sulphur. V. Cystein as an Intermediary Product in the Metabolism of Cystin.**

*Howard B. Lewis and Daniel A. McGinty, J. Biol. Chem., 53:349, Aug., 1922.*

The purpose of this paper is to report the occurrence of a cystein derivative in the urine after the administration of a nontoxic derivative of cystin in which complete oxidation of the molecule was prevented by "protecting" the amino-group by substitution. Phenyluraminocystin, usually in amounts of 1.0 gm., was administered to rabbits either per os or subcutaneously in water suspension or as the sodium salt and the urine was collected for 24 hours after the administration. In such urine the authors found there is present a substance which has been identified as phenyluraminocystein. This furnishes evidence, they say, that the first stage in the catabolism of cystin is conversion to cystein, with subsequent deamination and oxidation of the latter. In the case of the phenyluraminocystein, deamination has been prevented by conjugation and the cystein derivative is probably excreted as such in the urine.

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**Vitamins, Exposure to Radium and Intestinal Fat Absorption.**

*J. C. Mottram, W. Cramer and A. H. Drew, Brit. J. Exper. Path., London, 3:179, Aug., 1922.*

In the authors' experiments, rats that had been kept without food for 20 hours were used. They were then fed artificially at a given time by passing a narrow glass tube down the throat through which the food was introduced. The animals to be compared were fed at the same time and killed some hours later at the same time, the number of hours varying in different experiments from 2½ to 7 hours. Pieces of different parts of the small intestine exactly equidistant from the pylorus were cut out, fixed, stained, and examined in paraffin section. In the first set of experiments 2 batches of animals were fed, the control set on standard diet and olive oil; the other set on standard diet, olive oil and vitamin B, given in the form of marmite. The standard vitamin-free diet consisted of starch, purified casein and salt mixture. In a second set of experiments, cod-liver oil was used instead of olive oil, so that the animals received an ample supply of vitamin A. The effect of radiating the animals was next investigated.

The authors found that histochemic study of fat absorption from the intestine demonstrates that the functional activity of the intestinal

epithelium as regards absorption is profoundly affected by the presence of vitamins A and B (particularly the latter) in the food. These food-accessory factors have a stimulating action on intestinal absorption, and probably also on intestinal digestion, even in quite normal animals which have not been subjected previously to any special diet. On the other hand, in the absence of vitamins, there is no delay in the passage of food in such animals. After exposure to radium sufficient to produce a lymphopenia, the absorption of food is impaired in the same way as if vitamins were absent, and this effect cannot be counteracted by an abundant supply of vitamins in the food. These observations confirm the opinion previously expressed by the authors that lymphocytes play an important part in the absorption of food, and that the marasmus resulting from a deficiency of the water-soluble vitamin is due to an impaired absorption and assimilation of food from the intestine.

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**Organic Foods with Specific Action.**

*Emil Abderhalden and Ernst Gellhorn, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195: 1, June 19, 1922.*

Certain extracts derived from yeast and other substances, but especially the former, exert a favorable influence on alcoholic fermentation and on the consumption of oxygen by the cells and tissues. This action is particularly noticeable in cells and tissues of pigeons fed exclusively on rice and exhibiting the usual symptoms of alimentary dystrophy in consequence of this mode of nutrition: decreased body temperature and diminished gaseous exchange. The latter is at once strongly intensified in the cells of such animals by the addition of yeast products. Possibly the therapeutic and prophylactic effect of yeast in alimentary dystrophy is to be attributed to this influence exerted on cellular respiration. To investigate this question, the authors examined the effect of yeast preparations on smooth and striated muscles, namely on the gastrocnemius, the esophagus, the total heart (Straube), the heart muscle preparation (Loewe), and the bulbus of frogs. The yeast extracts employed were: (1) an aqueous extract obtained from dry yeast in the water-bath; (2) an alcoholic extract prepared in the same way; (3) an acetonie extract; (4) an alcoholic extract of yeast hydrolysate (hydrolysis of dry yeast with 10% sulphuric acid), which was separated into a water-soluble, an alcohol-soluble and an alcohol-acetone-soluble fraction; (5) a maceration juice from yeast, obtained by maceration with the threefold quantity of water at 37° C. and separated in the same way into 3 fractions; (6) an autolysate from dry yeast, which was separated by dialysis into 2 fractions; (7) a dialysate from the maceration juice; (8) an alcoholic extract from yeast, hydrolysate after hydrolysis with 5% hydrochloric acid. The examined muscles were suspended by means of small platinum hooks in Ringer's solution and stimulated by single induction shocks at intervals of 80 seconds. After the determination of the opening threshold, the yeast extract in question was added, its stimulating effect manifesting itself by the increased extension of the contractions and, if the effect was particularly strong, in the lowering of the opening threshold. The action of some extracts is exclusively

paralyzant, negatively inotropic, whereas others are able, in appropriate concentration, to increase the functional capacity of the striated, smooth, and cardiac muscles. This effect is also observed if the employed solutions are absolutely free from protein. The gastrocnemius shows a lowering of the opening threshold and an increase in the height of contraction, the distance between the coils of the sliding inductorium remaining unaltered. The esophagus shows first a paralytic stage with decreased tonus and without contractions, and then an intensive excitation of the smooth muscles, manifesting itself by increased tonus and by the greater frequency and sometimes also the increased extension of the contractions. In the heart preparations, the yeast extracts produced a considerable increase in the size of the pulse, often preceded by a short-lived diminution of the height of contraction, the positively inotropic effect reaching its maximum after 3 minutes. If the cardiac muscle preparation exhibits irregular contractions for lack of oxygen, a regularization is effected under the influence of the yeast extracts, together with an increase in the size of the pulse. Finally, mydriasis was provoked in the enucleated eye of the frog, either directly or by intensifying the adrenalin effect.

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**Organic Foods with Specific Action. XV. Feeding Experiments with Synthetic Foods and with the Simple Constituents (Bausteine) of the Organic Compounds Used as Foods, with and without the Addition of Nutramins.**

*Emil Abderhalden, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195: 199, July 4, 1922.*

The experiments of feeding animals with synthetic foods and with the simple constituents of such foods, were undertaken from various viewpoints and included not only the study of the body weight, but also that of the nitrogen metabolism. One of the reasons which prompted these laborious experiments was the consideration that where chemically pure and definitely characterized substances were used in feeding, the influence of the accessory foods should be very clearly and unequivocally shown, since the effects of any impurity could be definitely ruled out. Hence, the question resolved itself into this: Is it possible to maintain adult animals (for technical reasons rats and mice were chosen) in a state of metabolic equilibrium by feeding them the simple constituents of complex organic foods, with the addition of inorganic foods in their simplest form? The simple constituents were either synthesized and transposed into the form in which they occur in nature, or derived from natural products; in the latter case they were very carefully purified. The influence of yeast preparations on the outcome of these tests was then studied.

It is possible to maintain rats and mice for some time at an equilibrium of body weight and nitrogen metabolism, by means of synthesized simple constituents, plus mineral foods and water. But soon a deficiency of nutramins occurs; however, this can be readily supplied by the addition of small amounts of yeast, bran, rape-oil, cod-liver oil, butter and the like, thus not only preventing any loss of weight, but changing it to a gain. The same thing was noted where,

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in place of the synthetic simple constituents, those derived by hydrolysis from complex organic food-stuffs were used. Here also it appeared that the well-known food substances do not suffice to maintain the organism at the height of its functions. In growing animals, feeding with simple constituents was insufficient to maintain growth; in order to start it, it was necessary to add small amounts of yeast, butter or the like. This kind of food, composed purely of simple constituents with the addition of nutramins, is especially useful in determining the biologic valence of the separate amino-acids.

It appeared from these tests that L-tryptophan and, apparently, L-cystin are absolutely indispensable; their elimination caused severe disturbances of nutrition; likewise lysin, arginin and histidin seem to be irreplaceable. Norleucin and isoleucin can be replaced by ordinary leucin (amino-isobutylacetic acid). Where all the amino-acids of the C<sub>6</sub> series were wanting, a loss of weight occurred. The diamino-acids, asparaginic and glutaminic acid, also appear to be irreplaceable, while glycocoll, alanin, and oxyglutaminic acid can be replaced, at least during a limited time, such as was consumed by these experiments. The lack of purin and pyridin bases, as well as of cholesterin, seems to be without effect; possibly the experiments were not continued long enough to reveal any harmful influences. Animals kept on a cystin-free diet, which succumbed exhibiting the picture of alimentary dystrophy, showed a strikingly weak cystein reaction in their tissues, indicating that the cells were impoverished in cystin. Since the tissue cells contain a substance consisting of cystein and glutaminic acid, which plays an important part in oxidative processes (Hopkins), the cystin deficiency of the food apparently causes an interference with cell respiration.

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**Organic Foods with Specific Action. XVI. Comparative Researches on the Effect of Heated and Unheated Bran and Yeast, and of the Organs of Pigeons Normally Fed and Those Fed with Polished Rice.**

*Emil Abderhalden, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:432, July 21, 1922.*

The disturbances of cellular metabolism in pigeons fed with polished rice have been reported in previous communications. The marked diminution of oxygen consumption may be attributable to several causes. There may be a diminution of substances directly concerned in carrying out oxidation processes, such as coferments, activators and oxidation ferments; there may be a change in the cell content tending to interfere with the normal course of oxidation; or, possibly, the carbon dioxid elimination does not proceed along normal lines, and this leads, secondarily, to an interference with oxidation. Experiments were carried out with a view to deciding these questions. Pigeons kept on a diet of polished rice received at the same time the organs of healthy, normally fed pigeons. Control animals were on a rice diet, and also received the organs of pigeons fed with polished rice exclusively. No characteristic differences were found in the 2 sets of animals. A mixture of healthy organs offered some advantages in the treatment of spasms, and there was a rise in both the body tem-



perature and the gas metabolism; yet the animals finally succumbed. Possibly the amounts were insufficient, or they were administered at an unsuitable stage of the dystrophy. Two kinds of substances may be active, whose absence would give the picture of dystrophy. It is conceivable that there are special substances governing the new formation of tissue.

Other experiments sought to determine whether the dystrophic phenomena seen in rats kept on a one-sided diet, could be relieved by feeding the animals the meat or an organ mixture of normal pigeons. In a considerable number of animals no difference existed in the results produced by the tissues of normal or of diseased pigeons. In some cases better results were obtained by feeding with the healthy organs, while in others the diseased organs gave the better returns. At any rate, it appears from the experiments with pigeons that the cells require and contain very small amounts of the active substances, so that 1-2 gm. tissues are not enough to supply the requirements of the organism for them. It was of interest to decide whether polished rice was entirely devoid of these substances, or whether they were present in much reduced amount. It was possible to answer this question, because heating destroys the active substances. As a matter of fact, polished rice does contain small quantities of them. These unknown nutritive substances, or at least some of them, probably give off material for the production of definite bodies with definite action in the cells. But it is possible that each substance acts at the same time as an irritant and as a stimulant. The stimulus may possibly consist of nothing else than the establishment of conditions necessary for the course of a definite process.

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### **Organic Foods with Specific Action. XVII.**

*Emil Abderhalden and Ernst Wertheimer, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:460, July 21, 1922.*

Pigeons fed on polished rice are much more sensitive to lack of oxygen than normal animals. But it was not possible to explain this sensitiveness by deficient CO<sub>2</sub> elimination, for no interference with the elimination of CO<sub>2</sub> could be demonstrated. Presumably, oxygen respiration is directly concerned. As a matter of fact, the tissues of pigeons fed on rice give a strikingly weak cystein reaction, pointing to a diminution of the combination of cystein and glutaminic acid, which Hopkins has described and which is concerned in oxidative processes. In pigeons fed on rice, respiration is much slower and at the same time deeper, evidently in consequence of reduced susceptibility of the respiratory center. The effect of radiation was tried in such pigeons, since it is known that radiation increases the respiration of erythrocytes in sensitized blood. The same behavior was noted in these pigeons, but the effect was of short duration. The lowering of body temperature after parenteral administration of adrenalin, which was also observed in pigeons, cannot be influenced by pilocarpin, atropin and yeast preparations. The gas metabolism acts directly as the fall of temperature. In rice-fed pigeons, an injection of adrenalin produces a sudden fall in temperature, and death in a short time.

Like the normal bird, pigeons at an advanced stage of dystrophy are able to produce ornithuric acid (dibenzoylornithin) from benzoic acid. In dystrophic pigeons the heart action diminishes more and more, the number of heart beats falls to 100-120, but increases quite strikingly when yeast is added to the diet. In an advanced state of dystrophy the pigeons are much more sensitive to rotation than normal pigeons.

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**Organic Foods with Specific Action. XVIII. Experiments with Pure Foods.**

*Emil Abderhalden, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:480, July 21, 1922.*

In order to evoke the phenomena of alimentary dystrophy in pigeons, without feeding them on polished rice, the animals received the following mixture: 5 gm. of repeatedly purified casein, 10 gm. of absolutely pure maltose, 5 c.c. olive oil, or, in place of it, 1 gm. palmito-stearic acid, 1 c.c. oleic acid and 1 gm. glycerin; in addition thereto 5 gm. of a mixture of mineral substances (1 part each of magnesium sulphate, and iron citrate, 1½ parts each of sodium chlorid and sodium phosphate, 2 parts of calcium phosphate, 4 parts each of potassium phosphate and calcium carbonate, and 0.1 part each of sodium fluorid and sodium iodid). Pigeons fed with pills made from the above mixture, within a fortnight developed the same symptoms of severe dystrophy as those birds fed on rice. The addition of 0.5 gm. yeast sufficed to change the mixture into a food which maintained growth for a considerable period. This experiment excludes the possibility that alimentary dystrophy in animals fed exclusively on polished rice depends upon substances contained in the rice. It proves beyond a doubt that the condition is produced by the absence or the deficiency of certain substances in the food administered.

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**New Points of View in the Vitamin Problem.**

*Groebbels, Klin. Wchnschr., Berlin, 1:1548, July 29, 1922.*

The weight of an animal that is not given sufficient vitamins undergoes a slow and continuous decrease. But when the diet of tadpoles is changed by withdrawing vitamins there is a demonstrable increase in weight for more than a week. But a metabolism experiment gives more reliable and rapid evidence of the effect of avitaminosis. Such experiments by different authors have given varying results. Birds are most frequently used but are not adapted for gas exchange experiments, because CO<sub>2</sub> determination in birds cannot be used as a measure of metabolism; nor are birds suited for the experiments after they have developed spasms or paralyses from avitaminosis because it is difficult to judge the factor of motility. Hence the author made metabolism experiments on white mice; these show only weakness and loss of weight after a diet without vitamins. On oat feedings the oxygen values varied at most 10%. Under absolute fasting the fall in oxygen consumption reached its maximum after 24 hours, and after a few hours weakness developed. In animals who were first fed with oats and then with polished rice until death, there was gradual loss of about 30% in weight, as in the fasting ani-

mals. The absolute oxygen consumption increased 24-59% in the first few days, and later there was a decrease, which occurred earlier in heavy animals. A few days before death the animals showed a fall in temperature, sluggishness of movement and spasmodic flank respiration, and lay on their sides. If oxygen is administered at this stage the animals recover and remain alive longer than the control animals. When thymus substance was added to the vitamin-free diet, the oxygen consumption did not increase. The author believes that the vitamins are stored in the growing body. After the withdrawal of vitamins the stores are first used up, these being less in the growing than in the adult animal. The early increased oxygen consumption may be explained by the loss of an inhibiting substance or by a toxic action of a nonoxidized intermediate product. Secondary disturbance of salt and protein metabolism appears after the vitamin stores are used up and follows the same course as in death from starvation. The decrease in tissue respiration is probably not caused by the avitaminosis; the rise when vitamin extracts are given is probably brought about by substances which influence the salt and protein metabolism in a positive way, just as food does in fasting.

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**The Distribution of Vitamin B in the Wheat Kernel.**

*Marion Bell and Lafayette B. Mendel, Am. J. Physiol., 62:145, Sept. 1, 1922.*

To determine the distribution of vitamin B in wheat and its products, foods containing various percentages of wheat and wheat derivatives and comparable to each other in their content of all known dietary essentials except vitamin B were fed to albino mice, and the rate of growth on these foods was compared with normal rates. When the entire wheat kernel is thus used as the source of vitamin B in the diet, it was found that from 15-40% of the cereal is required to insure growth at a normal rate. Patent flour contained no appreciable vitamin; first clear and second clear displayed about the same concentration as the unmilled grain; low grade flour and bran were about twice as rich; standard middlings (which included the portion containing most of the embryo) were 4 times as rich as the entire grain. Hand-dissected portions of grains, representing more nearly the true structural divisions of both spring and winter wheat, were also investigated. Vitamin B was found in both embryo and endosperm. Finally, wheat grains were cut in half crosswise and equal quantities of the 2 ends were fed to different animals, but the rate of growth induced by both ends was practically the same.

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**On a Type of Ophthalmia Caused by Unsatisfactory Relations in the Inorganic Portion of the Diet. An Ophthalmia Not Due to Starvation for Fat-Soluble A, and Not Curable by Its Administration.**

*E. V. McCollum, Nina Simmonds and J. Ernestine Becker, J. Biol. Chem., 53:313, Aug., 1922.*

The authors repeatedly observed a type of ophthalmia in rats that were being provided with an abundance of fat-soluble A. Investigation led them to believe the ophthalmia was due to an unfavorable

relationship between certain inorganic elements in the food of the animals. From the data presented it is evident that the one constant factor which operated in the experimental ophthalmia was a high content of chlorin, although it is possible that a high sodium content in the diet may contribute to cause this pathologic condition. The authors make the tentative suggestion that these are the etiologic factors involved in inducing an eye condition, which may be easily confused with the xerophthalmia due to lack of fat-soluble A.

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**Studies on Experimental Rickets. XXI. An Experimental Demonstration of the Existence of a Vitamin Which Promotes Calcium Deposition.**

*E. V. McCollum, Nina Simmonds and J. Ernestine Becker, J. Biol. Chem., 53:293, Aug., 1922.*

Previous experimental work convinced the authors that existing methods were incapable of differentiating beyond doubt between fat-soluble A and a special calcium-depositing substance should such exist. Accordingly they formulated a plan which involved a comparison of a selected list of fats in respect to 3 kinds of effects in nutrition: (1) They tested cod-liver oil, shark-liver oil, butter-fat, and several vegetable oils for potency in causing the cure of xerophthalmia due to lack of fat-soluble A. (2) They made comparative tests of the same fats to determine their value in promoting growth in young rats which were restricted to a diet so low in calcium that satisfactory growth was not possible without the provision of some substance which would make for a greater efficiency in the utilization of calcium. (3) They further studied these same fats by means of a "line test" to discover their relative values for inducing the deposition of the line of calcium salts in rachitic bones. Graphic and tabulated data show that cod-liver oil oxidized for 12-20 hours does not cure xerophthalmia in rats but does cause the deposition of calcium in the bones of young rats which are suffering from rickets. This shows that oxidization destroys fat-soluble A without destroying another substance which plays an important rôle in bone growth. The authors found coconut oil to be lacking in fat-soluble A, since it will neither prevent nor cure xerophthalmia, but it contains a substance which stimulates the deposition of calcium salts in rickets in a manner similar to cod-liver oil. Cod-liver oil, shark-liver oil and burbot-liver oil were found to be highly effective for protecting the body against the effects of a calcium deficiency, for curing xerophthalmia, and for the deposition of lime salts in rachitic bones. The authors' experiments demonstrate the existence of a fourth vitamin whose specific property appears to be to regulate the metabolism of bones.

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**Experimental Rickets in Rats. VI. The Anatomic Changes Which Accompany Healing of Experimental Rat Rickets under the Influence of Cod-Liver Oil or Its Active Derivatives.**

*Alwin M. Pappenheimer, J. Exper. Med., 36:335, Sept. 1, 1922.*

The author describes the sequence of changes which accompanies the restoration of rachitic bone to an approximately normal condition.

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The first obvious effect of the administration of cod-liver oil or one of its active fractions in the ribs of a rat rendered rachitic by diet 84, is the deposit of calcium salts in the zone of preparatory calcification. Diet 84, described by Sherman and Pappenheimer, had been found satisfactory for therapeutic tests in that the preparatory cartilage remains permanently calcium-free for a period of at least 2 months, even when growth remains stationary. The deposition begins regularly in the lateral aspects of the cartilage, and extends across the cartilage as a broad band. Gradually, the area extends basally as far as the rows of proliferating cells, and distally it involves all the irregular prolongations throughout the rachitic metaphysis. Beginning calcification has been observed within 24 hours after an initial dose of pure cod-liver oil, and after 5-7 days, calcium is often present throughout the greater portion of the cartilage.

Accompanying the deposition of calcium in the matrix of the cartilage, there is a laying down of salts in the osteoid tissue. In the thickened perichondral osteoid, one finds a granular deposit beginning in the osteoid contiguous to the cartilage. As this osteoid tissue becomes transformed into fully calcified bone, the osteoblasts embedded in its substance change their character, becoming more pycnotic and angular and acquiring the stainable processes distinctive of adult bone corpuscles. With the calcification of the capsules and matrix of cartilage cells, there is an invasion from all sides by blood-vessels which bring about a resolution of the calcium and a digestion of the contained cellular material, exactly in the same way as this takes place physiologically during endochondral ossification, but more irregularly. This destruction spares the cells at the base of the cartilage, where the columnar alignment is preserved. These basal cells eventually form the new zone of preparatory calcification, when healing is completed.

The resorption of the excessive amount of osteoid, which also occurs on a large scale, is less easy to follow. However brought about, this resorption takes place first in the proximal half of the rachitic metaphysis, that is the portion nearest the cartilage, and only later affects also the distal portion. Accompanying the removal of excess cartilage and osteoid, there takes place an extreme and striking distention of blood-vessels. The study of anatomic changes cannot explain satisfactorily the mode of action of cod-liver oil. This subject is greatly simplified by the observation that the determining incident is the initial calcification of the preparatory cartilage and osteoid. The subsequent changes follow inevitably. The problem resolves itself, therefore, into the question of how the cod-liver oil promotes the deposition of calcium.

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#### **The Relations of the Vitamin Function to Calcium Metabolism.**

*K. Miyadera, Biochem. Ztschr., Berlin, 130: 199, June 20, 1922.*

The relations of the vitamin function to calcium metabolism have been frequently discussed on the basis of the Mellanbys' observation that young dogs fed on a diet deficient in the lipoid-soluble A factor show bone changes somewhat resembling those found in true rickets. In rickets the essential disturbance was assumed to be that the cartilaginous and connective tissue loses its capacity to bind calcium in



spite of an abundant calcium supply, and it was conjectured that vitamins induced the calcipexic function of the tissues. Whether the entire pathogenesis of rickets is explained by this will not be investigated here. For certain reasons it is improbable that rickets can be produced by vitamin deficiency alone. The demonstration of a cause of a disturbance by no means proves that this cause is the only possible one and that other causes might not produce the same phenomenon. On the other hand, clinical observations prove that the addition of vitamin to the diet effects improvement in calcium fixation in some cases of rickets. The author recalls that Freise and Rupprecht influenced calcium metabolism in rachitic children by administration of raw carrot juice. Hamburger and Stransky found that vegetable powders in incipient rickets improved calcium retention, though their results were not uniform. This appears to point to a nonuniform etiology of human rickets. Experimental rachitis, which has never been absolutely identical with spontaneous human rickets, may be produced by different interferences. Schloss's researches on the promotive influence of cod-liver oil on calcium retention come under this category.

All clinical experiments in rachitic children lacked the prerequisite that the metabolic disturbance which was favorably influenced by vitamin administration had in reality been produced by a vitamin deficiency. The prerequisite for these experiments was hypothetic, and the hypothesis of this prerequisite was to be proved by the experimental result. Further, in rickets there is often spontaneous improvement, which lessens the conclusiveness of the experimental result. For this reason it appeared desirable to the author to study this question under unassailable conditions. As has been said, young dogs fed on a diet deficient in the lipoid-soluble vitamin A show bone changes that resemble those occurring in true rickets. Hence, further experiments were undertaken on dogs. Vitamin was found to promote the retention and assimilation of calcium. A positive calcium balance is not excluded on a vitamin-free diet, but the experiments on the relations of vitamin function to calcium metabolism show the correctness of Bickel's theory that vitamin confers on body cells their capacity for assimilating the inorganic substance. Assimilation is possible to a certain extent even without vitamins but it is insufficient, so that the body finally succumbs despite adequate caloric nutrition.

## RESPIRATORY SYSTEM

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### **Measuring Respiration with Gasometer and Valves.**

*Martin Gildemeister, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:96, June 19, 1922.*

Although the ordinary gasometer is suitable for the determination of the volumes of respiration as well as of the vital capacity in animals on account of its low resistance, it is much too voluminous. The author therefore devised a small gasometer of celluloid, distinguished by low respiration resistance and small volume. The construction of the respiration valves is similar to those devised by R. du Bois-Reymond and Katzenstein. The gasometer for animals of medium size has a celluloid drum measuring 16 cm. in diameter and 6 cm. in depth, each rotation corresponding to 420 c.c. The drum is provided with

4 strips of copper, to which sliding brushes are adjusted, for the electric registration of the rotations. The respiration resistance, with a passage of air amounting to 600-1000 c.c. per minute, corresponding to the respiratory capacity of a normal cat, is very small, about 2 mm. water. The valves consist in small celluloid caps, measuring 8 sq. cm. in transverse section and weighing 0.6 gm., which float on a layer of mercury, 4 mm. in thickness. It is advisable to place the gasometer within the respiratory passage.

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**A New Type of Recording Spirometer.**

*R. Burton-Opitz, J. Lab. & Clin. Med., 7:681, Aug., 1922.*

The type of spirometer which has been made use of by the author registers the volumes of the respiratory air as a continuous line on the smoked paper of a kymograph. Since the action of its different parts may be reversed at any time, it may be employed to record a practically unlimited number of respiratory cycles. The resistance resident in its different parts is so slight that the subject of the experiment scarcely perceives any hindrance to the flow of the respiratory air. A very simple change in the adjustment of this apparatus enables the experimenter to register solely the volume of the tidal air or solely that of either the inspiratory or expiratory air. Details of the apparatus and its use are given in connection with an explanatory diagram.

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**A Modification of the Microrespiratory Apparatus.**

*Bohumil Krajník, Biochem. Ztschr., Berlin, 130:286, June 20, 1922.*

This modification of the microspirometer, the construction of which is based on a combination of the principles embodied in Winterstein's and Krogh's microrespiratory apparatuses, is employed in the analysis of gaseous exchange in lower organisms. The advantages are that it has no stop-cocks; the receptacle is detachable; its sensitiveness is very great; the petroleum index and the mercurial column are not easily broken, and accuracy and rapidity are obtained in reading pressure differences. The connection of the receptacles with the branch tubes and the terminus of the index tube arms is much more appropriate.

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**Pleural Pressure.**

*H. Müller, Virchow's Arch. f. path. Anat., Berlin, 138:157, June 14, 1922.*

Donders' pressure difference (less pressure in the pleura than in the lungs) is said not to exist in unborn or new-born infants before the first breath. Bernstein thinks that there cannot be negative pressure in the pleura of the fetus or else the fetus would drown in its own amniotic fluid by aspirating it. He forgets that the lung of the fetus is not breathing, and that if it were filled with amniotic fluid it

would not matter, as it could be removed by absorption or with the first expiration. From experiments in insufflation of air into the lungs of still-born infants, Bernstein concludes that the negative pressure which did not exist there before but can be demonstrated afterward, is caused by the expansion of the lung. He thinks that this proves that normally the expansion of the thorax with the first inspirations produces Donders' pressure difference; that the later inspirations take place from a higher level of equilibrium, after the first respirations have caused a lifting of the ribs, which, as a result of overstretching of the elastic apparatus which brings about expiration, is no longer equalized on expiration. Herrmann denies this overstretching theory. He asserts that in new-born infants who had died shortly after delivery but who have doubtless breathed, there is no difference of pressure; that Donders' pressure difference only develops with progressive growth, as the thorax grows more than the lung. He cites Lehmann's animal experiments in confirmation of this opinion. But the author thinks that these experiments are not sufficient for proof.

The author himself has measured the pleural pressure in the lungs of 14 new-born infants which were found on autopsy to be completely empty of air and found negative pressure almost without exception. In only 2 cases was there equal pressure in 1 pleural cavity (infants 20 cm. and 35 cm. long); in the latter there had been aspiration of amniotic fluid which had brought about an increase in volume of the lung and thus equalization of pressure. The negative pressure in the pleura can only be explained as being due to a disproportion between the size of the thorax and the size of its contents, a disproportion that cannot be overcome by the air pressure on account of the rigidity of the thoracic wall. But this disproportion does not develop after birth, but during fetal life. It is due to defective firmness of the thoracic wall in new-born weak infants, that the thorax cannot follow the inspiratory movement of the muscles; the same effect is produced later by loss of firmness of the thorax caused by rickets. This is why rachitic children are in special danger from bronchopneumonia and bronchitis.

Contrary to Herrmann's assertion, 22 measurements made by the author prove that thoracic aspiration does not begin after birth and that in the cadavers examined, pressure values do not change with increased age of the infants. The rise of pressure which appears on tracheal measurement after opening of the pleural space is due to the elastic contraction of the lung. It may be prevented by total synechia of the folds of the pleura or by the alveoli being filled with exudate. Parts of the lung distended compensatorially with air may lose their elasticity by overstretching. By stopping up the trachea, the action of the elastic pressure of the whole lung is prevented; by stopping up one bronchus, only that in the affected section of the lung. That the tracheal pressure in adults is greater than that in children is due to the fact that the elasticity of the lungs increases with increasing physiologic demands upon it by a corresponding strengthening of the elastic tissue.

Placzek asserts that the demonstration of negative pressure in the pleura shows that the child has not breathed. According to what precedes, this theory is false. That Placzek's experiments always agreed

with his theory, the author thinks is due to errors in his method of measurement.

On the outer side of the thorax is the air pressure ( $A$ ); counter-pressure is furnished by the elasticity of the thorax ( $T$ ) + the internal pressure on the thorax, consisting of the air pressure decreased by the elasticity of the lungs ( $E$ ). It results, therefore, that  $A = T + (A - E)$ ; from this it follows that  $T = E$ . A thorax emptied of air cannot support the external pressure of the air. All the ribs were broken when the trachea of a dog was suddenly connected with a flask in which the air pressure was reduced to 6 cm. Hg. In processes of contraction, it is not the traction of the cicatricial tissue but the external air pressure which causes the sinking in of the wall of the thorax.  $T$  and  $E$  increase under physiologic conditions on inspiration and decrease on expiration. But if, for instance in tracheal stenosis, the air tension in the alveoli is increased, the lung elasticity may be decreased by overstretching. The value of the pressure of the air enclosed in the lung,  $A^1$ , decreases by  $E = A - A^1 - E = A - T$ . According to this, the elasticity of the thorax is not at all affected ( $T = 0$ ) as in open pneumothorax, where the external air pressure acts fully on the inner surface of the thorax and where the elasticity of the lung is excluded (emphysema). If in tracheal occlusion  $A^1 - E > A$ , and therefore positive pressure prevails in the pleural space, then during expiration  $T < 0^1$  and the wall of the thorax must protrude outward.

In chronic stenosis, the above-described picture may be brought about by valve respiration (Pfanner). The respiratory movement in increase of intrapulmonary pressure means a great yield of work with little application of power, as a renewal of air in the lung is only possible by the production of a negative pressure. Intrapulmonary rise in pressure plays a great part in bronchopneumonia in childhood, because the relative smallness of the bronchi gives it support. On the other hand, filling of the alveoli with inflammatory exudate may lead to increase of pleural pressure. In all cases in which he could demonstrate positive pleural pressure in the cadavers of new-born infants, the author found the cause in the above-named conditions. He thinks, therefore, that the measurement of pleural pressure even in cadavers gives important information, though pressure measurements on the living, which are quite harmless, may be expected to give better results.

## NEUROMUSCULAR SYSTEM

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**The Cerebellum as the Center for Regulating Sympathetic Muscle Tonus. Preliminary Report.**

*K. Kure, T. Shinosaki, M. Kishimoto, U. Fujita and M. Sato, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:525, July 21, 1922.*

Experiments conducted on 51 dogs showed a homolateral diminution of muscular rigidity after extirpation of one-half of the cerebellum with reduction of the tendon reflexes. Within a few days this phenomenon is rendered indistinct by a compensatory increase of muscular tone. Injections of adrenalin produce an increased rigidity on the side operated upon and an increased patellar reflex in excess of the normal. Participation of the sympathetic nerve is suggested not only by the

increased rigidity under the influence of adrenalin, but also by a diminution of creatin content in the muscles of the side operated upon. When the declive of the vermis is stimulated, slow contraction of the homolateral muscles is produced, affecting chiefly those of the neck, back and ears. The latent period is relatively long, and the irritation persists without any appearance of action currents. The characteristic contraction of the neck muscles is absent after extirpation of the cervical sympathetic nerve with the stellate ganglion. The authors conclude that the cerebellum must be regarded as the center regulating sympathetic muscle tone; the proprioceptive reflexes pass to it along Gowers' and Flechsig's tract, while centripetal impulses reach it through the nucleocerebellar tract from the labyrinth and possibly also from the third ventricle. Governed by these impulses, the cerebellum regulates sympathetic muscle tone. The connections with the cerebrum permit a support of voluntary movements by sympathetic muscle tone indirectly through the cerebellum.

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**Early Movements, Reflexes and Muscular Reactions in the Human Fetus and Their Relations to the Fetal Nervous and Muscular Systems.**

*M. Minkowski, Schweiz. med. Wchnschr., Basel, 52:751, July 27, 1922.*

Mechanic muscle excitability persists longer than movements and reflexes arising under nervous influences. Tested by direct percussion it is found first that some muscles contract much more readily and constantly than others, for example the biceps and pectoralis in the upper extremity, but the contraction also extends to neighboring muscles. The difference in excitability is attributed to the difference in the time when their structural differentiation took place, which has been proved histologically. Contractions are also produced by pressure, crushing or stretching of the muscles. The great lability of rhythm is especially noticeable in the fetal heart as well as its dependence on temperature. The fact that the muscles are directly stimulatable after removal of the spinal cord proves their independence of the embryonic medullary tube. Stimulation of the different roots of the spinal nerves causes movement in the regions supplied by them; mechanic stimulation of the cranial nerves at the base of the medulla oblongata effects repeated movements of opening and closing the mouth. Removal of the cerebral hemispheres does not influence skin, tendon and motor reflexes, removal of the midbrain weakens them. The reflexes described, of the trunk, neck and extremities of the fetus seem, therefore, to be essentially spinal in nature. On the other hand, the labyrinth reflexes are localized in the medulla oblongata. Attention is called to the histologic structure of the fetal nervous system, for instance, to the absence in young fetuses of complete medullary sheaths in the spinal marrow and in the nerve trunks.

The reflexes in adults possess in potential form all their fetal and infantile characteristics, particularly their variability and their capacity for generalization. The presence of the labyrinth reflex shows an early complete differentiation of the vestibular apparatus when the



fetus is not more than 4 cm. long. From the physiologic standpoint the coexistence of 2 types of motor phenomena in the fetus is noteworthy: (1) phenomena of a primitive muscular type; and (2) movements and reflexes of a nervous type. From the physiologicopathologic point of view there is a tendency, especially on the basis of Monakow's work, to conceive of different disturbances in lesions of the central nervous system as due to partial regressions to earlier stages of phylogenetic and ontogenetic development, without forming a simple repetition of them. The irradiation of reflexes, the extension of the reflexogenous zones and the appearance of phenomena of spinal automatism and of reflex inhibition are to be explained in this way.

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**Diverse Sensibility in the Successive Excitations of Single Tactile Organs.**

*Alessandro Gatti, Arch. ital. di psicol., Turin, 2:28, June 30, 1922.*

For his investigations, carried out on himself, the author chose the side of the left pulse, surface in part deprived of hairs, in which the tactile organs are represented by the corpuscles of Meissner; the tactile points are here distributed in the quantity of 12-44 per centimeter. As stimuli he used the exciting hairs according to the method of M. von Frey, measured in tension value expressed in grams per millimeter of radius, that is to say, the weight represented by the maximum of force of flexion of such a hair, established on the chemical scale, divided by the median radius of the transverse section of the hair. The apparatus used was first a special extensometer, later an instrument especially constructed, consisted of 2 small vises placed one above the other, united by means of a spring, which are able to reciprocally approach or separate by means of a screw, permitting minimum variations in the length of the hair. The determinations were made with normal stimuli, 1-8 gm. per millimeter. Horsehairs were employed.

The author was able to state, as a result of his investigations that, the law of Weber was verified in the most exact manner in the successive excitations of single tactile organs.

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**Electric Stimulation of the Skin.**

*U. Ebbecke, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:300, July 21, 1922.*

The electric current is capable of stimulating not only the cutaneous nerves, but also the epithelium of the epidermis. The study of the phenomenon may start with 3 symptom groups: the irritation phenomena subjectively perceived, the alterations of the condition of the skin objectively noted, and the peculiar alterations of electric resistance. Since the constant galvanic current exerts only a weak direct stimulation, it was conducted to the skin through 2 fluid electrodes, glass tubes containing sodium chlorid or Ringer's solution and having an internal diameter of 1.3 cm. During current closure, a sensation in the nature of a brief dull and very slight stroke is observed at the cathode only, with a current of 0.2-0.4 ma. At the anode no opening sensation is

experienced until 1 ma. is reached. The conditions here conform with the law of Pflüger.

A current strength which does not produce a direct closing or opening effect, will produce a slight sensation of itching, becoming more apparent with the duration of the current and limited to the area of skin below the electrode. Stimulation of the epidermis itself is involved, i. e. there is a pressure sensation, as a symptom of tissue irritation. At the anode, the irritated area, which has remained pale, shows numerous minute depressions of the skin, while at the cathode can be seen a number of pale elevations, in part corresponding to the hair follicles. Electro-endosmosis is clearly illustrated thereby. A wheal is produced at the anode only when the current is high enough to give rise to distinctly painful sensations. Redness and wheal formation are stronger at the cathode; they disappear at the end of an hour, while the anode redness remains vivid. Hyposensitiveness exists at the cathode, hypersensitiveness at the anode. The cathode is the stronger stimulus in its immediate effect, the anode in its after-effects. If, instead of an indifferent electrode fluid, an acid or an alkaline solution be employed, the acid solution will produce a stronger anode effect, while the alkaline fluid will have a greater cathode effect. The influence of the iontophores is illustrated by this.

This behavior likewise shows the independence from nerve stimulation, since there is no opening or closing effect, but the intensity and duration of the current go hand in hand with an otherwise unknown delay of reaction increase and duration of reactive after-effects. Pflüger's law does not apply to this cell stimulation, as is known from the stimulation of unicellular organisms and of taste cells. These findings may be related to Bethe's theory of the alteration of H and OH. To study the changes in resistance, a stronger stimulating current was sent through the skin by means of like fluid electrodes, and the resistance of the former anode and cathode areas was determined by means of a weak measuring current. From such tests, conclusions can be drawn as to the effect of the electrolyte upon the cell membranes. The skin as a whole, as well as each single epidermal cell with its plasma membrane, acts as a membrane. K ions tend to relax, Ca ions to contract the cell membrane. H ions vary in their effect, according to their concentration, contracting in low, and relaxing in higher concentrations. If 2 fluid electrodes of varying acidity are used, the skin may at will serve as a rectifier in either direction. Alkalies applied to the skin, even without current, tend to reduce the resistance. Experiments with adrenalin showed that the cutaneous resistance is independent of the filling of the blood-vessels. Introduced electrically, histamin is well suited for the production of wheals; it acts specifically as a capillary poison upon endothelial cells and their permeability.

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**Alterations of the Membrane and the Fleischl Phenomenon.**

U. Ebbecke, *Pflüger's Arch. f. d. ges. Physiol.*, Berlin, 195:324, July 21, 1922.

Local stimulation can materially reduce the cutaneous resistance against direct current. Cellular stimulation can be measured by this

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means and its course followed. Physical considerations in connection with this start from the fact of polarization. By this the current

strength does not follow Ohm's law but the formula  $i = \frac{e - \epsilon}{w}$ ,  $\epsilon$  being

the electromotive resistance. That is, when the polaric maximum has been reached, with a further increase of tension the resistance increases less rapidly than the current strength,  $\epsilon$  disappearing as against  $e$ . Thus a current of high tension apparently has a lower resistance than one of low tension. These facts apply to the skin. For demonstration, a sliding inductorium was used, because with it the opening stroke is produced by a current of about 5 times the tension, in about one-fifth of the time, than is the closing stroke. When a nerve (Fleischl) or the skin (Gaertner) is switched into the secondary current, the galvanometer will indicate a preponderance of the opening stroke. It is a question whether the Fleischl cutaneous effect is altered after cutaneous stimulation. The electrodes were fluid electrodes described in a previous article. A slowly vibrating needle galvanometer was used to measure the relative amount of current. If the effect depends upon polarization and local cutaneous stimuli affect the membranes, then a change must necessarily result. As a matter of fact, the difference between the closing and the opening stroke was always lessened, and both were better conducted after stimulation, although the increase was greater for the closing than for the opening stroke. These findings support the view that the Fleischl phenomenon is a polarization effect, and that the local galvanic reaction of the skin is an alteration of membrane. Alterations of the membrane, i. e. increased permeability, also serve to explain that the threshold for the Fleischl phenomenon is higher for a nerve fatigued by strong stimulation than for a fresh nerve.

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### **The Innervation of Chromatophores Based on Antagonistic Stimuli.**

*R. H. Kahn, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:337, July 21, 1922.*

It is assumed that the pigment cell is made to contract into a sphere by stimulation of its sympathetic nerve supply, and that the cessation of the stimulus causes the cell to expand, this corresponding, then, to the resting stage. Instead of this, an equilibrium of antagonistic innervations might be assumed. Such antagonistic innervations would have to be demonstrated, the possibility of doing which is given by the study of adrenalin action. From 0.2 to 0.5 c.c. of 1:10,000 solution of adrenalin exerts a maximal clearing action upon the melanophore cells of the frog which begins in 20 seconds. The action of adrenalin in producing spherical contraction of these cells exceeds all other effects which might take place simultaneously. The effects of nicotin are quite different. Suitable doses of nicotin produce in frogs a prolonged darkening, evidently due to the elimination of the vegetative innervation. Variations in the results of the

experiment are due to the coaction of other factors (light, temperature, moisture, condition of the circulation, and internal conditions which cannot be determined). Pilocarpin exerts a characteristic effect on the chromatophores in the nature of an expansion. This effect is especially brought out in *Hyla arborea* after severing the optic thalamus from the corpora bigemina. Thus adrenalin and pilocarpin produce opposite effects upon chromatophores. Both poisons attack peripherally, that is, in the cell or very near it, for their action persists even after the central nervous system is destroyed; when circulation is interfered with, their effect is limited to the area of injection. *Hyla* and *Rana esculenta* show a change of color under different influences. According to the condition of the melanophores, other chromatophore cells are more or less obscured. Adrenalin also causes a change of color, exhibiting a similar opposite effect; adrenalin causes an expansion of the yellow pigment granules of the lipophores. Stimulation of the sympathetic corresponds in its effects to the action of adrenalin, parasympathetic stimulation to that of pilocarpin. Parasympathetic stimulation causes the pigment of the melanophore cells to expand, that of the lipophore cells to contract; sympathetic stimulation produces the reverse effect. The condition of pigment in the chromatophores at any one time represents a state of equilibrium between the antagonistic nerve stimulations. Those animals which persistently remain light are under a persistent parasympathetic stimulation. At present nothing is known of the paths of parasympathetic innervation of the chromatophores. Presumably both stimuli travel over the same peripheral path.

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**The Cutaneous Galvanic Reflex in Cats and Dogs (So-Called Psychogalvanic Reflex).**

*Yuzo Hara, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:288, July 4, 1922.*

Continuing the studies of the galvanic cutaneous phenomena of the frog conducted by Schilf and his collaborators at the Institute, the same methods were used in curarized cats and dogs, artificial respiration being supplied. The deflection was made from the hind paws or the forepaws. Among the stimuli there were acoustic, optic, tactile, and those of pain. In addition, faradic stimulation of 1 nerve was also used. In 2 tests, older dogs gave no reaction upon direct stimulation of the ulnar or the median nerve. Among 4 young dogs, 1 showed a definite psychogalvanic reflex only in response to acoustic stimuli; the other 3 did not respond to sensory stimuli, but to direct irritation of the nerve. It cannot be determined whether this reflex is essentially the same as that appearing after sensory irritation. Among 10 cats, 9 regularly responded with a psychogalvanic reflex to optic, acoustic and tactile stimuli, i. e. curare does not interfere with sensory activity in cats. In man, the psychogalvanic reflex depends on the activity of the sweat glands; in the frog, upon that of the cutaneous glands. The author's findings in dogs agree with the observations of Luchsinger on the behavior of sweat secretion on the naked paws.

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**The So-Called Psychogalvanic Reflex Phenomenon in Frogs and Its Relation to the Vegetative Nervous System.**

*Erich Schiff and Albert Schuberth, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:75, June 19, 1922.*

These experiments were carried out with Wheatstone's bridge, the current generator consisting in a lead accumulator and the registration apparatus in a moving coil galvanometer, manufactured by Siemens and Halske, with a sensitiveness of  $0.23 \times 10^{-8}$  amperes per centimeter of the scale. The applied stimuli were almost exclusively pain stimuli (touching with a hot metal point) in addition to tactile and optic stimuli. The experiments were made on specimens of *Rana esculenta* caught in October. Under the conditions stated, a galvanic reflex deflection is produced by pain stimuli even in paralysis induced by curare, if it is not too severe, but not always by optic and tactile stimuli. Intensive pain stimuli do not fail until a dosage of curare 30 times as large as the paralyzing dose has been reached. Nor is the capability of the frog to react to tactile, optic and algetic stimuli by psychogalvanic reflex deflections abolished by decerebration; the pain reflex is observed even after the removal of both optic lobes, though not the reaction to optic stimuli. The galvanic reaction may occur quite independently of the spinal conduction, since it was found possible to provoke it in the posterior extremities on stimulation of the anterior ones after severing the spinal cord. But the reaction is abolished by severing the sympathetic chain on the level of the sixth vertebra. The reflex was obtained even with the ganglionic chains forming the only connection between the anterior and posterior portions of the animal, i. e. after ligating the aorta and severing the vertebral column as well as the cutaneous, muscular and nervous bridges. The centrifugal part of the reflex arc takes its course within that central portion in the spinal cord up to somewhere above the fourth vertebra, after which it passes into the sympathetic chain and through the rami communicantes into the ischiatic nerve, from which it proceeds to the cutaneous glands. As a rule, the reflex is abolished by the removal of the optic lobes and by a lesion of the medulla oblongata. The centers must be located between the cerebellum and fourth vertebra, the inferior portion of the medulla oblongata probably playing the most important part, since, in 1 case, the reflex was observed even after the removal of three-quarters of the medulla. The centripetal portion of the reflex is formed by the sensory conduction. The reflex may be employed for the investigation of cerebral localization in frogs and of pharmacologic effects on the cutaneous glands.

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**The Function of the Ninth Dorsal Motor Nerve Root.**

*Gotthard Söderbergh, Acta med. scandin., Stockholm, 56:677, No. 6, 1922.*

The author has been able to study the effects, in 2 cases, of stimulating the ninth dorsal motor nerve root electrically. During the



course of laminectomy, the motor root was isolated within the dura mater. Previous studies on other nerves are thus continued, and the following plan of innervation is offered: Fifth dorsal, the first segment of the rectus abdominis. Sixth dorsal, first and second segments of the rectus abdominis. Seventh dorsal, the rectus abdominis above the navel, and the highest part of the external oblique. The sixth and seventh dorsal have probably some distribution to the highest part of the transversalis. The eighth dorsal chiefly innervates a strip of the external oblique extending from the ninth and tenth ribs toward the navel, but is also distributed to a strip extending from the rectus above the navel, and from the lateral abdominal musculature to a point just below the navel. The ninth dorsal is the principal motor nerve of the transversalis at the level of the navel, shares in the innervation of the middle part of the lateral muscles of the abdomen and is also distributed to the rectus below the navel. The tenth dorsal is a main motor nerve of the internal oblique and of a strip of the external oblique inserted on the eleventh and twelfth ribs and innervates the transversalis below the navel and the rectus below the navel. The eleventh dorsal is the principal motor nerve of the rectus below the navel. The twelfth dorsal and first lumbar nerves innervate the rectus below the navel and the lower portions of the lateral muscles of the abdomen.

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#### **Visceral Sensibility.**

*A. Fröhlich and H. H. Meyer, Ztschr. f. d. ges. exper. Med., Berlin, 29:87, July 21, 1922.*

The authors reëxamined the question of visceral sensibility, because Lehmann had thrown doubt on the validity of Bell's law with respect to the conduction of pain from the abdominal viscera, having observed complete analgesia of the abdominal organs in the case of a dog after severing the anterior roots and leaving the posterior ones intact. But this may be attributed to an error of technic, since the painlessness may have been caused by the employment of enormous quantities of novocain-adrenalin for anesthetization in severing the roots and in performing laparotomy on the same day. The authors tested the sensory paths in the abdominal viscera by 27 experiments (severing of the roots, the splanchnic nerves). For the excitation of pain in the bladder, electric stimulation was employed; the intestine was distended by the introduction of a rubber balloon, in addition to the provocation of spasmodic contraction by intraperitoneal and intra-arterial injection of barium chlorid. Anemia (injection of adrenalin) does not excite contraction and pain. The experiments showed that pain is conducted from the bladder by the pelvic nerves to the posterior sacral roots, and from the intestine by the greater splanchnic and the hypogastric nerves to the posterior roots, principally at the thoracic level. In other words, the visceral conduction of pain to the spinal cord is performed exclusively by the vegetative system and through the posterior roots, the anterior roots playing no part in it whatever.

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**Has Intrathoracic Bilateral Division of the Truncus Sympathicus an Influence on Gastric Secretion?**

*B. Ishido, Biochem. Ztschr., Berlin, 130: 151, June 20, 1922.*

In his research on the sequels of vagotomy, Lithauer communicated experiments from which it appears that the secretion of gastric juice is altered after bilateral intrathoracic vagotomy above the diaphragm. This alteration is manifested by a lengthening of the secretion curve after a definite test-meal and by a slower initial rise of the curve. The subsequent course of the curve shows irregular ascents and descents, while the total amount of gastric juice measured in Pawlow's stomach is considerably above normal. Finally, the stomach shows continuous secretion, i. e. juice is secreted even in an empty stomach. From all this it appears that the vagus trunk sends inhibitory fibers into the thorax, and failure of these to function explains increased secretion for the most part. Simultaneous exclusion of secretagogue fibers, the presence of which in the vagus is rendered probable by Pawlow's experiments, is expressed at most by the slow initial rise of pathologic secretion curves. It seemed desirable therefore to ascertain whether bilateral intrathoracic division of the truncus sympathicus influences the secretion of gastric juice. The results disclosed only a slight inhibitory influence. The duration of secretion was not shortened and the amount was only slightly diminished. Conversely, in Lithauer's experiments, bilateral vagotomy produced considerable increase of secretory action. The degree of inhibition does not correspond to the extent of this increase. Obviously the stomach receives sufficient inhibitory fibers by another path so that sympathicotomy has only slight influence. It is noteworthy also that bilateral intrathoracic division of the truncus is possible with unilateral exposure of the thorax.

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**Experimental Proof of the Conductivity of Pain through the Sympathetic System in Intestinal Colic.**

*F. Brünning and Gohrbrandt, Klin. Wchnschr., Berlin, 1: 1657, Aug. 12, 1922.*

After paralyzing the celiac plexus of the cat and dog with nicotin, the severest intestinal colics induced by barium chlorid were absolutely painless. Irritation, however, of the spinal elements by traction on the mesentery gave rise to pain. Inasmuch as nicotin paralyzes only the sympathetic elements and leaves the spinal nerves intact, the absence of pain during very severe intestinal colic after the use of nicotin is proof that the sensation of pain in intestinal colic is conveyed through sympathetic tracts from the intestine.

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**The Nervous Control of the Urinary Bladder in Amphibians.**

*F. J. F. Barrington, Brain, London, 45: 126, June, 1922.*

Experiments were undertaken to determine whether the normal evacuation of the urinary bladder in amphibians depended on the

integrity of some part of the anterior end of the hind-brain, as has previously been shown to be the case in the cat. The animals used were the common frog, the common toad, the crested newt and the spotted salamander. Removal of the forebrain only, with 1 exception, was never followed by an overdistended bladder; the exception was a salamander and after hardening the midbrain was found to have become softened. In all cases where the transection was behind the cerebellum an overdistended bladder resulted. With the exception of 1 newt, on which not much reliance can be placed owing to the small size of the brain, all cases where the transection went between the cerebellum and midbrain resulted in an overdistended bladder. With the exception of 1 frog, whose entire midbrain was found softened, no experiment resulted in an overdistended bladder where the transection went through the anterior half of the midbrain.

A transection through the posterior half of the midbrain was only made in 1 frog, and in it the bladder was not overdistended. If, therefore, as is probable, the result in the newt alluded to was an error in observation, the overdistended state of the bladder observed in all 4 species is due to the destruction of some part of the posterior half of the midbrain. This localization approximates to that already described in the cat. In the cat, however, paralysis of the bladder was shown to be present; in amphibians the overdistension might be due to this or to failure of the closing mechanism to relax. Another possibility might be that the ureters do not open directly into the bladder, i. e. that the overdistension might be due to some abnormal rate of filling of the bladder. The latter possibility, however, can be easily disproven by mere inspection, because in normal frogs it can readily be seen that the bladder is emptied when urine is passed by the disappearance of the translucent area in the bladder region, whereas in animals with overdistended bladders, even though considerable amounts of urine may escape during struggling when the animal is handled, a large translucent area in the bladder region persists. Though there is no direct evidence that failure of the bladder to empty is due to its paralysis, it seems unlikely that it is dependent on a tonic contraction of the sphincter because, as has already been stated, in animals with overdistended bladders comparatively slight mechanical causes can lead to the expulsion of considerable quantities of urine from the cloaca, though the bladder is still overdistended at the end.

In studying the effect of division of the spinal cord and its roots, it was found that in the frog and toad, both the anterior and posterior sets of roots must be divided to produce overdistension of the bladder; from this it follows that the impulses from the posterior part of the midbrain which normally prevent overdistension must pass out through both sets of nerves. In 2 newts, division of the cord at the eighth and tenth vertebrae respectively resulted in an overdistended bladder. In 3 salamanders the cord was divided, and in all an overdistended bladder resulted. In 1 the level of transection was the fifteenth root, the fourteenth being the most anterior large root to the hind-limb plexus; in the other 2 the level was the sixteenth root, and the fifteenth and sixteenth respectively were the first large roots to the hind-limb plexuses. It is, therefore, probable that if an upper set of bladder nerves exists in the salamander, only the lower set conveys impulses

from the posterior part of the midbrain to the bladder, in which case the salamander differs from the frog and toad in this respect and resembles the cat.

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**The Relations between Innervation and Chemism of Striated Muscles. I. The Creatin Content of Skeletal Muscles in Decerebrate Rigidity and Other Forms of Nervous Overstimulation.**

*J. G. Dusser de Barenne and D. G. Cohen Tervaert, Pflüger's Arch. f. d. ges. Physiol, Berlin, 195:370, July 21, 1922.*

The existence of postglandular vegetative fibers in striated skeletal muscles has been positively demonstrated. The fibers are centrifugal, but bear no relation to muscular tone. Pekelharing and his collaborators have assumed that the creatin chemism of a muscle is affected by the vegetative nervous system. In order to test these claims, either the spinal or the autonomous stimulation alone was cut off from the musculature, and the creatin content of the muscles under consideration was determined, either alone or in combination with hyperinnervation. The present paper deals with the effect of decerebration rigor and of phasic stimulation upon the creatin content; the second communication is concerned with the influence of the autonomous nervous system. In all, 76 tests were carried out, 5 in dogs, and 71 in cats. The total creatinin was determined according to Pekelharing, or to Folin.

In the first series of tests, the cerebrospinal motor innervation of the gastrocnemius of one hind paw was cut off by severing an anterior root lying caudad from the fourth lumbar vertebra. The brain was then removed, and the comparative determination of creatinin carried out a few hours later. No difference was found between the two sides. In other tests, one gastrocnemius was removed before decerebration and its creatin content compared with that of the other muscle after decerebration. Here, also, no increase of creatin was found. Decerebration rigor does not lead to an increase in creatin. Pekelharing and Hoogenhuize experimented with unilateral division of the posterior root and concluded that when the proprioceptive fibers of a group of muscles were ruled out, the amount of creatin in those muscles diminished. To study the effect of phasic stimulation, one gastrocnemius was removed and its creatin content taken as a standard. The spinal cord was then cut at the first cervical vertebra and a contralateral rhythmic flexure contraction of the intact extremity was produced by prolonged rhythmic faradic stimulation of the central stump of the divided N. peroneus. No clear cut and unequivocal effect on the creatin content of muscles is produced by phasic hyperstimulation. Finally, both types of hyperstimulation were combined. In all 9 tests of this series the creatin content of the stimulated muscle increased. Analogous to these findings, apparently, are those of Pekelharing and Hoogenhuize, who observed an increase of creatin in frog muscles when these were immersed in solutions increasing muscular tone; under these conditions the gradual development of contracture results in a sort of continued contraction and tremor of the muscle which exist alongside of each other for a certain time.

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**The Physiology of Stepping.**

*T. Graham Brown, J. Neurol. & Psychopath., Bristol, 3: 112, Aug., 1922.*

*Production of Rhythm.*—In a previous article Brown has shown that the rhythmic alteration of movement in stepping is not produced by the action of rhythmically timed stimuli evoked in the moving limbs themselves. The rhythm is essentially produced in the nervous centers. The essential condition of stepping is the production of 2 antagonistic activities (flexion and extension) of continuous type and of more or less equal intensities in the spinal centers. Other investigators have accepted this view. They have, however, translated it to mean that the rhythm arises under equality of excitation and inhibition evoked in each group of motor neurons. But the inhibition and excitation given by the same stimulus are not equal, and the inhibition given by extension-producing stimuli is less nearly equal to the excitation than is the inhibition given by flexion-producing stimuli to the excitation given by them. Simultaneous rhythmic movement in 2 antagonistic muscles is, however, one of the chief factors of stepping, and the author has found that if excitation and inhibition are nearly equal in 1 group of motor neurons, the rhythm is best marked in the other muscle. Therefore, the condition of rhythmic discharge is not equality between the inhibition and excitation playing upon each group of motor neurons. The rhythmic movements are of greatest magnitude and most complete in type when the 2 resultant discharges are of greatest intensity, while remaining equal.

*Bilateral and Unilateral Stepping.*—Sherman's theory of the mechanism of stepping is founded on the assumption that excitation and inhibition given by the same stimulus are equal. The author has measured the intensity of the 2 reflexes and it appears that the exact opposite takes place in experiments on the decerebrate cat. Stimulation of one and the same afferent nerve in a limb gives flexion in the same limb and extension in the crossed limb of the pair. If the stimuli are progressively increased in intensity from threshold up, the crossed extension rises at a steeper gradient than the same-sided flexion. It attains its maximum while the same-sided flexion is still moderate, or even weak. Further increase in the intensity of stimulation gives further increase in intensity of flexion, while extension merely remains minimum or diminishes a little. Brown's theory also explains how stepping may occur in one limb alone while the other is flexed or extended.

ENDOCRINE GLANDS

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**Studies of the Substances with Specific Action Produced by Various Organs. VIII.**

*Emil Abderhalden and Olga Schiffmann, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195: 167, June 19, 1922.*

These experiments are concerned with modifications of the metamorphosis of tadpoles of frogs and toads effected by thyroid substance

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and by the substances obtained from the thyroid gland by complete decomposition. The authors' investigation further extended to certain substances whose structure is perfectly known, namely 3,5-diiodo-l-tyrosin, 3,5-diiodotyramin, the dipeptid glycyl 3,5-diiodo-l-tyrosin,  $\beta$ -iodopropionic acid, iodo-acetyl-3,5-diiodotyrosin, 3,5-diiodotyrosin methylester and iododihydroxyl propane (alival, with 63% iodine). In investigating the modification of the metamorphosis of animals and plants by certain substances, attention must be paid not only to the alteration of the external form but also to the development of the various organs and tissues. The authors further propose to examine various iodized protein substances with respect to their effect on the metamorphosis and to compare the latter with that of diiodotyrosin. One point they wished to settle was the question whether it is possible to exert an influence on the development by the administration (partly oral and partly parenteral) of thyroid substances or other iodine compounds before the deposition of the eggs. Animals of both sexes having been treated in this way, spawn and roe were brought into contact with each other (1) from treated males and untreated females, (2) from treated females and untreated males, and (3) from both sexes equally treated. These experiments have not led to any serviceable results so far, in consequence of unsatisfactory spawning on the part of the females. The animals were kept in permanently aerated water; the authors give a detailed description (with illustrations) of the ventilation apparatus. After the administration of thyroid substance, transformations in the liver (thick and dark pigment layers) were observed in addition to the usual modifications of the metamorphosis. The degenerated intestinal epithelium was not cast off into the intestinal lumen, but was left behind the new epithelium in the shape of brown degenerating round cells. This pigment is probably transported to the liver by migratory cells. The liver is greatly diminished in size. After the administration of fresh thyroid, the animals do not live long enough to complete the metamorphosis: they retain the tadpole type up to the last; the only organ whose metamorphosis is completed is the intestine. The forelegs do not break through; the mouth is changed, but not transformed into that of a frog. If advanced tadpoles are fed on thyroid, they become decidedly more similar to frogs metamorphosed in the normal way, but do not attain the normal size; the tail is almost reabsorbed, the transformation of the mouth reaches a higher degree, and the shape is more similar to that of a frog. Tadpoles treated during the earlier stages react more slowly than the older animals and do not complete their metamorphosis but become deformed. Strumas and Basedow-strumas affect tadpoles of toads (*Bufo*) only slightly, if at all; the reaction of these larvae to thyroid hydrolyzed with sulphuric acid was equally slight, whereas the tadpoles of frogs (*Rana temporaria*) behaved in the typical way. Diiodotyramin and diiodotyrosin had the same effect as thyroid on the tadpoles of either. Here again the effect is the more pronounced the earlier the stage during which it is exerted—beginning with the undifferentiated anlage of the hindlegs. Diiodotyrosin and diiodotyrosin methylester, derivatives of iodotyrosin, produced the same effect as the latter, whereas iodo-acetyl diiodotyrosin,  $\beta$ -iodopropionic acid, alival and tyrosin proved ineffective.

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**The Effect of Pancreatic Extract (Insulin) on Normal Rabbits.**

*F. G. Banting, C. H. Best, J. B. Collip, J. J. R. Macleod and E. C. Noble, Am. J. Physiol., 62: 162, Sept. 1, 1922.*

The rabbits used in these experiments were fed on a diet of oats and hay. The sugar in the blood was determined by the Schaffer-Hartmann method. At the termination of the observations, whenever possible, the glycogen in the liver was determined by Pflüger's method, using the Schaffer-Hartmann method to determine the sugar after suitable dilution of the hydrolyzed glycogen solution. The usual procedure was to take a sample of normal blood and then inject the insulin in several places subcutaneously, after which further samples of blood were taken at regular intervals. The animals were meanwhile kept under constant supervision. It was found that the subcutaneous injection of purified alcoholic extracts of pancreas (for which the authors suggest the name insulin) caused the percentage of sugar in the blood to fall within a few hours. With the fall in blood sugar the rabbit exhibits highly characteristic symptoms, the earliest of which are signs of hunger and thirst, hyperexcitability and apparent fear. In the majority of cases exhibiting convulsions the blood sugar was found to be about 0.045%. Subcutaneous injections of dextrose solutions were found to antidote these symptoms so that the animal was fairly normal in a few minutes.

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**Effect of Insulin (Pancreatic Extract) on the Sugar Consumption of the Isolated Surviving Rabbit Heart.**

*J. Hepburn and J. K. Latchford, Am. J. Physiol., 62: 177, Sept. 1, 1922.*

Authors found the average sugar consumption of the isolated rabbit heart perfused with Locke's solution to be 0.87 mg. per gram per hour. When insulin of proved potency, as tested by its ability to lower the blood sugar in normal rabbits, was added to the perfusion fluid, the average sugar consumption rose to 3.06 mg. per gram per hour. The average glycogen content of the treated and untreated hearts was practically the same.

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**Morphin Hyperglycemia and the Adrenals.**

*G. N. Stewart and J. M. Rogoff, Am. J. Physiol., 62: 93, Sept. 1, 1922.*

In a previous article the authors have shown that the hyperglycemia associated with etherization, asphyxia and piqure is not essentially dependent upon the liberation of epinephrin from the adrenals, since it can be obtained, and apparently in as high a degree as in normal animals, when the adrenals have been removed or the epinephrin output from them interfered with. In this work an experimental hyperglycemia was produced with morphin, after various adrenal operations had been performed (removal of both adrenals in rabbits, removal of one adrenal with denervation of the other, or of one adrenal and a large portion

of the other with denervation or destruction of the medulla of the remaining fragments in cats and dogs). The tabulated results of the experiments record the initial rectal temperature before administration of morphin and the maximum (or minimum) temperature observed thereafter; the initial blood sugar content and the maximum content after morphin; the final blood sugar content and the effect produced upon it by a period of intermittent asphyxia; the percentage of glycogen in the liver at the end of the experiment and the body weight and the dose of morphin sulphate per kilogram of body weight.

A study of these data shows that hyperglycemia is much less commonly induced by morphin in cats which have recovered after removal of one adrenal and denervation of the other, or after removal of one adrenal and a large portion of the other, with or without denervation of the remnant or destruction of the medulla of the remnant, than in normal cats or in those which have recovered from such operations as splenectomy. When morphin causes hyperglycemia in cats after such adrenal operations, the maximum increase in the blood sugar percentage is on the average much less than in normal cats, and is more slowly reached. Dogs, after removal of one adrenal and denervation of the other, behave in the same way as cats in regard to the frequency with which morphin hyperglycemia may be elicited. In rabbits which have survived double adrenalectomy and are in good health, the same difference (in the frequency and degree of the hyperglycemia induced by morphin) between the adrenalectomized and the normal animals is seen as exists between cats subjected to the adrenal operations described and normal cats. The results show that the asphyxia hyperglycemia, as was previously demonstrated for that form of hyperglycemia, as well as for that due to etherization and to piqure, is in a high degree independent of the adrenals. The morphin hyperglycemia in this regard is therefore sharply differentiated from the other forms of experimental hyperglycemia mentioned.

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**The Suprarenals and Morphin Intoxication.**

*Juan T. Lewis, Semana méd., Buenos Aires, 29:309, Aug. 10, 1922.*

Lewis replies to Soler's comments and claims that the theory of auto-intoxication in animals after suprarenal capsulectomy which Soler defends, has been discarded by recent authors as antiquated. Soler's claim that there is a "morphinizing" toxin in such dogs has not been confirmed by other authors. Instead of hypo-excitability, as reported by Soler, Lewis observed merely a diminution of excitability in the case of one dog, whose arterial pressure was decreased to 4.5 cm. The cortex remained excitable. Cheyne-Stokes' rhythm, which Soler observed, was never present in Lewis's cases. Unlike Soler, Lewis considers that the morphin intoxication observed is due to the anesthetic. He also failed to observe a regressive effect on the part of the morphin. The excitability of the motor cortex decreased gradually as death approached, corresponding to the decrease in all the branches of functional activity. The loss of excitability was not an initial symptom specific of suprarenal insufficiency.

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**The Mechanism of Parasympathetic Glycemia.**

*Bornstein and Holm, Klin. Wchnschr., Berlin, 1:1695, Aug. 19, 1922.*

To answer the question of the relation of parasympathetic glycemia to the suprarenals, experiments were made on dogs and rabbits. The suprarenals were removed by laparotomy; the animals recovered very rapidly after the operation but died after a few hours quite suddenly with symptoms of increasing weakness, decreased reaction to external stimuli, difficulty in breathing and finally cessation of respiration. The heart continued to beat for a while. This complex of external symptoms was accompanied by a fall in blood sugar and liver glycogen; but death was not due to the fall in blood sugar; it occurred in cases where the blood sugar content was relatively high, as well as in cases where it was very low. The same is true of the glycogen content of the liver. But liver glycogen and blood sugar are connected with each other to the extent that a relatively high glycogen content is always accompanied by a rise in blood sugar at the moment of death, as blood sugar determinations after cessation of respiration showed. The hyperglycemia observed in normal animals after subcutaneous injection of pilocarpin can also be caused in rabbits and dogs with the suprarenals removed. Blood sugar fall and terminal rise, liver glycogen and death of the animal show the same regular relations as in animals with the suprarenals removed and not treated with pilocarpin.

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**The Repair and Activation of the Thyroid in the Hypophysectomized Tadpole by the Parenteral Administration of Fresh Anterior Lobe of the Bovine Hypophysis.**

*Philip E. Smith and Irene P. Smith, J. Med. Research, 43:267, June-July, 1922.*

Using amphibian larvae, the authors were able to demonstrate a marked interrelationship between the thyroid and pituitary glands. If the thyroid gland of a specimen from which the epithelial anlage of the pituitary has been removed at an early larval stage be examined some weeks or even months after this, it will be found strikingly atrophic, as distinguished from a normal, robust colloid-filled gland. This anatomically atrophic and functionally inactive condition is due to developmental fault rather than to actual regressive change. By the intraperitoneal injection of fresh bovine hypophysial substance, the atrophic thyroid can be brought back to normal. By varying the amount of mammalian pituitary substance all types of thyroid development can be induced, from extreme atrophy to hypertrophy and hyperplasia.

The tadpoles ranged in length from 25 mm. to the maximal larval size. By means of a 0.5 c.c. record syringe with a special attachment, injections were made of bovine pituitary substance, aseptically prepared, starting with 0.003 c.c. Injections were given 3 times a week in doses gradually increasing to 0.02 c.c. or more. As a control fresh muscle substance prepared in the same manner was injected. Injections of the pars intermedia or the posterior lobe were without effect. Only the anterior lobe substance evoked thyroid response. Metamorphosis of the hypophysectomized tadpole after treatment with anterior

substance was considered an indication of thyroid activity. That metamorphosis was not due to the direct effect of the hypophysial substance is certain since thyroidectomized tadpoles when injected with anterior lobe do not undergo metamorphosis. Attempts to repair the thyroid after hypophysectomy by feeding with pituitary substance failed completely; the specimens failed to metamorphose and the thyroid presented the typical atrophic condition. The results indicate that success in the treatment of human cases of hypopituitarism depends not on the oral administration of larger doses of pituitary substance nor in evolving a different method of preparation for oral administration, but in securing some extract of the anterior lobe which contains the active principle of this gland and can be administered parenterally.

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**Experimental Study of the Internal Secretion of the Ovary in Parabiatic Animals.**

*Naoshi Goto, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94: 124, July 28, 1922.*

After Sauerbruch and Heyde, interesting experiments on parabiosis were made by several authors, among them Matsuyama. In this series of experiments 2, and also 3, white rats were united; one pair is still alive  $2\frac{1}{2}$  years after the operation. When a normal female was united with a castrated animal, the ovaries increased to 10 times their original size, the uterus changed into a thin-walled cyst containing a clear fluid. The latter grew gradually, filled the entire abdomen and formed adhesions with the intestine. The contents of the uterus became purulent. This seems to have been due to the castration of the one animal. After the operation the mode of life must not be changed. When a semicastrate (1 ovary removed) was united to another animal the remaining ovary grew; there was no change in the uterus. When two semicastrated females were united no change was perceptible, but when a castrated and a semicastrated female were joined, the remaining ovary grew. After union of 2 castrates there was pronounced atrophy of the other sexual organs. The changes in the uterus were doubtless brought about by some substance that circulates in the blood of the castrated animal as a result of the operation. Afterward blood from the castrates was introduced into the bodies of normal animals. Both ovaries and uterus changed in the manner described before. There must therefore be some substance in the blood of castrates that is absent or present only in traces in normal blood. This substance has a direct or indirect effect on the ovary and causes the peculiar change in the uterus. The latter seems to be secondary since after the union of 2 castrates the uterus becomes atrophic in a few days.

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**The Functional Significance of the Testicular Interstitial Cells.**

*Z. Frankenberger, Anat. Anz., Jena, 55: 545, Aug. 10, 1922.*

The theory of the endocrine function of the interstitial cells founded by Bonin and Ancel received support particularly from the



labors of Tandler, Gross, Steinach and Schaffer but also encountered opponents (Plato, Mazetti, Stieve) who regarded them as "salivary" organs for the nutrition of the germ-cells. In serial sections of lizards' testicles, after fixing with osmium (Flemming), the author found very dark fat, especially at 2 spots, namely (1) in the interior of the seminiferous tubules, preponderantly directly around the lumen, and (2) in the interstitial cells. These cells are situated in the spaces formed by the junction of 3 or 4 seminiferous tubules (otherwise the seminiferous tubules lie close together) together with a few connective tissue-cells and with mostly very narrow centrally situated arteries and veins, or also merely capillaries. They generally have an eccentric nucleus with a large nucleolus, coarse alveolar protoplasm and vacuoles. The nucleus is very poor in chromatin; neither the author nor others have observed karyokinesis; the darkened fat globules were situated directly at the membrana propria of the tubules. That the membrane has preformed gaps as stated by Plato is not wholly denied by the author who has never seen them. Not infrequently he found fat globules also in the membrana propria itself as well as immediately on the other side of it in seminiferous tubules, a condition which appears to him to point to the nutritive significance of the testicular interstitial cells.

## **1b. BIOLOGIC AND ORGANIC CHEMISTRY**

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**Interfacial Phenomena, with Especial Reference to Colloids and Enzymes.**

*W. M. Bayliss, Bull. Johns Hopkins Hosp., 33: 307, Sept., 1922.*

In this Herter Lecture at Johns Hopkins Hospital, Bayliss refers to the need of better understanding of the problems of colloidal physical chemistry, illustrating his remarks with examples of unsolved problems in this field as they apply to physiology. Colloids are substances composed of separate ingredients or phases very finely divided, which are in contact but do not mix. These phases will present surfaces to each other, and at these surfaces there are of course forces of surface tension and of electric charge. Applying these facts to specific cases, adsorption is first discussed, with the conclusion that the nature of the forces at work in this phenomenon is as yet unsolved. Adsorption is clearly not entirely of chemical nature; it is probably, in part, an electric effect. Again, in regard to colloids like hemoglobin, many of the obscure relations may be thought of as due to effects of surface electric charge.

Enzyme action may be subject to explanation as an adsorption phenomenon. Certainly the action of enzymes is exerted at interfacial surfaces. The phenomena of enzyme action are cases of catalysis in heterogeneous systems. An interesting example given is that of urease (soy bean extract) which is active in alcohol, in which it is insoluble. Another proof is given by adding to a colloidal enzyme preparation some other colloid which will be adsorbed in part and thus lower the available surface of the enzyme. The reaction then proceeds much

more slowly (to a complete finish, however) and this reduction in rate has a negative temperature coefficient, which is characteristic of adsorption phenomena.

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**The Production of Electric Currents in Living Tissues.**

*H. Rohonyi, Biochem. Ztschr., Berlin, 130:68, June 20, 1922.*

In a previous communication on ionic permeability and membrane potential, the source of the force (E.M.F.) of the cupric ferrocyanid membrane was studied. As is known the system:  $\text{CuSO}_4$  solution | cupric ferrocyanid membrane |  $\text{K}_4\text{FeCy}_6$  solution, connected with a galvanometer by means of normal potassium chlorid—calomel electrodes, gives a potential of about 0.1 volt, in which the copper solution is negative and the ferrocyanid solution positive. The amount and direction of this system's E.M.F. are largely independent of the concentration of the copper and ferrocyanid solutions but are altered materially if the potassium chlorid content of the potassium electrodes is altered. Rohonyi propounded the theory that E.M.F. of the precipitated membrane is a diffusion E.M.F. which is to be calculated from the respective Planck's formula. In these chains the membranes possess the significance of a nonelectrolytic medium. Contrary to Beutner, who advanced a series of objections, it is shown that correct models of bio-electric phenomena are to be sought for not in Beutner's oil systems, but in precipitated membranes. The conclusions drawn therefrom regarding the structure and properties of the physiologic plasmahaut therefore remain correct.

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**The Relationship between Adsorption and Electrolytic Dissociation.**

*M. A. Rakusin, Biochem. Ztschr., Berlin, 130:282, June 20, 1922.*

In 1899 Lagergreen showed that porous substances in aqueous solutions cause negative adsorption, that is, they take up not a part of the dissolved substance, but the solvent (water). He found for example that negative adsorption takes place when dissolved chlorids come in contact with charcoal, kaolin, glass powder, etc. To confirm this, experiments were carried out with aqueous solutions of sodium chlorid and cane sugar. A piece of a clay plate served as adsorbent. It was shown that kaolin takes up only water in both cases. Thereby Lagergreen's phenomenon is demonstrated. It may be explained by assuming that in sufficiently dilute solutions of electrolytes not the salts, but the respective ions are present, which are not adsorbed. The tendency to dissociation arrests adsorption. In the case of electrolytically dissociating substances every possibility of adsorption is excluded entirely, as only undissociated molecules are subject to adsorption, as with colloidal solutions. For this reason such solutions, unless they are electrolytes, show irreversible adsorptions.

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**The Acidity of Certain Organic Decoctions.**

*Franck L. Soler and Virgilio Tedeschi, Semana méd., Buenos Aires, 29: 144, July 20, 1922.*

The acidity of decoctions of organic tissue which normally gives a neutral reaction has been attributed to the prolonged boiling and sterilization, which produces decomposition of the protein substances, with the formation of aggregates in which the carboxyl groups are not completely saturated. It is known that water or water-vapor at a high temperature produces phenomena of hydrolytic dissociation of proteins, even in the absence of mineral acids or proteolytic ferments. It is probable, though not certain, that the process may effect the separation of all the elemental constituents of the protein molecule, i.e. the amino-acids. It is not certain why this process of protein disintegration is so marked in the case of organic decoctions. It is simple to extract nucleoproteins from organs; these are soluble in water and saline solutions, and have a distinct acid character. The organs generally employed for therapeutic decoctions are those most rich in nuclear cells (thymus, pancreas). The nucleoproteins obtained in this manner are always associated with lecithin, with which they form adsorption complexes when precipitated with acids. The presence of nucleoproteins in the decoctions partially explains the acid reaction, but not the high degree of acidity.

The authors' experiments were for the purpose of determining the actual acidity of the decoctions, as expressed in the hydrogen-ion concentration. Instead of the usual colorimetric method of determination, which is purely empirical, the electrometric method was employed, with the use of a hydrogen electrode. The pH is equal to the logarithm of the reciprocal value of the hydrogen-ion concentration. This value decreases with the acidity. The value to be experimentally determined is the difference of potential of the hydrogen electrode, or rather the difference in potential between a nonpolarizable electrode of calomel (Oker Blom-Ostwald) and the hydrogen electrode.

The hydrogen electrode used in the test was absolutely accurate, with a nucleus of pure gold, covered with platinum-black by electrolysis by means of a solution of platinum chlorid. Although the recipient of the hydrogen was not hermetically sealed, complete saturation, corresponding to the atmospheric pressure, was sufficient for an abundant current, produced by a Kipp apparatus. Tests of the liquid obtained by decoction of the spleen gave an average of pH, 5.79, which constitutes a remarkable degree of actual acidity.

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**The Question of Asymmetric Synthesis.**

*L. Pirak, Biochem. Ztschr., Berlin, 130: 76, June 20, 1922.*

The methods of preparing asymmetric combinations have been designated as (1) synthetic and (2) analytic by E. Fischer and Markwald. These methods represent only those which aim at preparation of the d- or l- form of an optically active substance by synthesis, and those which strive to isolate, or to obtain an excess of, one component of racemic substances by the decomposition or alteration of

the other component. Asymmetric synthesis was attempted by employing circumpolarized light in accordance with Mascart's method. The attempt was unsuccessful.

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**An Analysis of Camel's Colostrum.**

*Helen L. Fales, J. Biol. Chem., 53:339, Aug., 1922.*

The author obtained and analyzed a sample of the colostrum of a bactrian camel, 2 days after parturition. In appearance it was thick and rich, not yellow but creamy white. It had a bland taste and no unpleasant odor. In reaction it was slightly amphoteric to litmus, acid reaction more marked. The specific gravity was 1.038. The chemical composition was: fat 7.4%; sugar 4.2%; protein 5.4%; casein 4.1%; albumin 0.5%; globulins 0.8%, and small quantities of ash and mineral salts.

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**The Diagnosis of the Proteins and Their Derivatives by Means of Color Reactions.**

*M. A. Rakusin, Biochem. Ztschr., Berlin, 130:268, June 20, 1922.*

The biochemical importance of some color reactions, such as the biuret reaction, Millon's and the xanthoproteic reactions, is much greater than that of color reactions as a whole. Certain atomic groups correspond to every color reaction of the proteins. A clear conception of the chemical nature can be gained only from a knowledge of a color reaction complex. Therefore the most important animal and vegetable proteins and their derivatives, i.e. the ferments and toxins, were studied comparatively as regards their behavior toward color reactions. The following reactions were employed: biuret, Millon's, xanthoproteic, Liebermann's, Adamkewitsch's, Molisch's, Pettenkofer's, Ostromilensky's reaction with picramic acid, Vohl's so-called blood sulphur reaction, and Rakusin's reaction for detecting chondroitin-sulphuric acid with barium chlorid. Of the color reactions Molisch's and Pettenkofer's are tests for carbohydrates, the others being tests for nitrogen. Millon's reaction is a test for the hydroxyphenyl group. The xanthoproteic reaction depends on the nitration of aromatic bodies, so that a negative result points to absence of phenylalanin, tyrosin and tryptophan. Liebermann's and Adamkewitsch's are tests for tryptophan. Of the protein reactions, which may be divided into 3 groups (nitrogen, carbohydrate and sulphur reactions), a definite complex of reactions corresponds to each protein substance which not only characterizes it but in some cases (chondrin) also indicates how the complete analysis should be carried out. In the case of substances containing chondroitin-sulphuric acid the latter must be removed by means of aluminum hydroxid before thorough hydrolysis of the substance.

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**A New Combined Method of Fractionating Proteins and Their Derivatives.**

*M. A. Rakusin, Biochem. Ztschr., Berlin, 130:432, July 20, 1922.*

In albumoses and peptones, the molecules of the natural proteins

are decomposed to such an extent that further fractionation by means of suitable ferments suggests itself. Hofmeister, Pick and Zunz, Fraenkel and Langstein attempted the fractionation of proteins from digestion products. The experiments on the natural proteins and ferments and their fragments, which must contain carbohydrates besides polypeptids, were to elucidate the following questions: (1) qualitative examination of proteins and ferments in regard to their behavior toward alcohol; (2) quantitative examination regarding the same property; (3) qualitative; and (4) quantitative examination of peptones in the aforementioned direction; and (5) combined fractionation of protein substances by methods of extraction and adsorption. The first experiments showed that alcohol withdraws nitrogenous substances (requiring further investigation) and carbohydrates from proteins with the exception of keratin. Only carbohydrates are withdrawn from fibrin, nucleo-albumin, casein or legumin. The proteates of ammonium and of the alkali metals behave toward alcohol the same as the corresponding proteins. Keratin surrenders no soluble substances to alcohol; ferments behave like full value proteins; only in the case of yeast is the extract free from carbohydrates.

If the extracts are treated with animal charcoal or aluminum hydroxid, the amino-substances reacting with Ostromyslenski's reagent are combined chemically and no crystalline carbohydrates remain in the filtrate. With peptone, which yields the 8 familiar color reactions, only 6 of the latter were obtained, namely, biuret, Millon's, Adamkiewicz's, Ostromyslenski's, Molisch's and Pettenkofer's. The extraction residue contains a substance which yields only Liebermann's reaction for tryptophan; the extract, a substance giving Adamkiewicz's reaction. Four-fifths of the pepsin-fibrin-peptone went into solution. By tedious procedures, extraction was continued until the individual extracts were colorless. The previous extracts were allowed to stand 24 hours with 10% by weight of aluminum hydroxid. The first filtrate yielded all extract reactions excepting Millon's; the second filtrate on further treatment with aluminum hydroxid lacked the biuret reaction; the third filtrate, Ostromyslenski's; the fourth, Adamkiewicz's; the fifth showed only Molisch's and Pettenkofer's. The aqueous solution of the extraction residue was also treated with aluminum hydroxid and it was found that the alcohol-insoluble part of the fibrin-peptone consists of a substance taken for tryptophan, which however lacks Adamkiewicz's reaction; and of ash constituents of the original peptone. The 5 nitrogenous peptone fractions correspond to the amino-acids obtained by means of thorough hydrolysis. Qualitatively, fibrin appears to be a full value protein. The described property of elective affinity seems to be exhibited by aluminum hydroxid particularly in alcoholic solution.

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**The Abiuret Albumin Nitrogen in Cow's Milk and Human Milk.**

*Mader, Klin. Wchnschr., Berlin, 1: 1555, July 29, 1922.*

All albumin substances down to the amino-acids give a blue to violet color with ninhydrin, if in addition to a free amino-group there is a free carboxyl group. The author endeavored to determine qualitatively and quantitatively the dialyzable protein substances in different

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sorts of milk, particularly cow's milk and human milk by means of a colorimetric method based on the ninhydrin reaction. Ultrafiltrates gave more constant and higher values than dialysates. Milk serum does not give any of the known albumin tests, not even the biuret reaction and the traces of ammonia often present in cow's milk must be removed by vacuum distillation. The milk must be absolutely fresh and nothing but neutral red solutions can be used. The reaction optimum only appears when the H-ion concentration of the solution to be examined remains constant; after the addition of a buffer, the reaction is most pronounced; the best substance for this purpose is a mixture of potassium monophosphate and sodium biphosphate. Neutral red is used as an indicator; and as colorimetric solutions, solutions of asparaginic acid with a known nitrogen content. The filtrate must be diluted, as otherwise the color tone will fall outside the colorimetric series.

The results of the experiments showed that cow's milk contains 18-21 mg., and human milk 51-60 mg. abiuret nitrogen, which can only be attributed to amino-acids. That it is a question of essential nitrogen and not of catabolized albumin or casein is shown by the fact that freshly drawn human milk contains 3 times as much aminonitrogen as cow's milk at least 1 day old.

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**Creatinin and Creatin in Muscle Extracts. III. Concerning the Presence of Enzymes in Muscle Tissue Which Have Creatin and Creatinin as Their Substrates.**

*Frederick S. Hammett, J. Biol. Chem., 53: 323, Aug., 1922.*

The extracts used in these experiments were made from the striated muscles of mature albino rats of both sexes. The muscle tissue was ground in a meat chopper, macerated with fine sand and an equal weight of Tyrode's solution, and 10 c.c. toluene added. The juice was then squeezed from the mixture by a filter press. The resultant extract was diluted with an equal volume of Tyrode's solution and 5 c.c. portions were used for the analyses, which were made by methods previously described by the author. The temperature of the incubator was maintained at 38°. All the recorded values for creatinin and total creatinin are averages of duplicate determinations. Those for creatinin represent the so-called "preformed creatinin"; those for total creatinin, the preformed creatinin plus the creatin as creatinin. The detailed tabulated and graphic data show that creatinin and creatin are easily dialyzable substances. The transformation of creatin to creatinin in muscle extracts is a reaction of the first order, which is masked in its early stages by changes taking place in the state of the colloids of the extracts. Hammett concludes that no enzyme participates in the transformation of creatin to creatinin in muscles because (1) the amount of creatinin formed in dialyzed extracts is but slightly greater than that formed in the dialysates of such extract; (2) the increased creatinin formation in noncentrifuged extracts, as compared with centrifuged extracts, on incubation is also small; and (3) the rate of creatinin formation in boiled extracts is no less than that of unboiled extracts.

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**The Influence of Position and of Temperature upon the Reaction of Aliphatic Amino-Nitrogen with Nitrous Acid.**

*Max S. Dunn and Carl L. A. Schmidt, J. Biol. Chem., 53:401, Aug., 1922.*

Dunn and Schmidt found that the rates of deamination of the  $\alpha$ -amino and of the  $\epsilon$ -amino groups of certain amino-acids are, between 0 and 30° C., markedly influenced by temperature. They observed that lowering of the temperature decreased the speed of deamination of the  $\alpha$ -amino group (of alanin) but did not totally inhibit the complete liberation of nitrogen from the  $\epsilon$ -amino group of lysin. The influence of the position of the amino group with respect to the carboxyl group in certain other amino-acids upon the time required to yield their nitrogen quantitatively was also studied, and it was found that increasing the distance of the amino group from the carboxyl group necessitated a longer period of time in order that a quantitative yield of nitrogen might be obtained.

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**The Fate of Some of the Phenylacetylated Amino-Acids in the Animal Organism.**

*George J. Shiple and Carl P. Sherwin, J. Biol. Chem., 53:463, Aug., 1922.*

The authors prepared phenylacetyl derivatives of the natural amino-acids: glycocoll, alanin, leucin, glutamin, glutamic acid, asparagin, aspartic acid, and ornithin. The substances were fed to or injected into dogs, rabbits, chickens, and human beings. In every case the results showed that when the amino group is phenylacetylated, complete or even partial catabolism of the amino-acid is prevented, thus demonstrating the impossibility of the formation of glycocoll from a more complex amino-acid under these conditions. The authors also observed that although different species detoxicate phenylacetic acid according to entirely different reactions, which yield completely different compounds, yet these products pass unaltered through the organisms of animals other than those in which the original detoxication occurred.

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**Preparation and Analysis of Animal Nucleic Acid.**

*P. A. Levene, J. Biol. Chem., 53:441, Aug., 1922.*

Levene has modified his older picric acid method for preparing animal nucleic acid by substituting colloidal iron for the picric acid. The new process consists in dissecting the glands (10 lb.) free from fat, grinding in a chopping machine, and transferring them into 5 L. water, containing 250 gm. sodium hydroxid. The mixture is boiled for 35 min. and then neutralized with acetic acid. Then 50 c.c. of a colloidal iron solution (iron dialyzed, 5%  $\text{Fe}_2\text{O}_3$ , Merck) are added and the solution is filtered and allowed to stand over night. To the filtrate is then added a double volume of methyl alcohol containing 2% of hydrochloric acid. The precipitate thus formed is filtered off

and washed with methyl alcohol until the filtrate is free from hydrochloric acid. This process was applied to the preparation of nucleic acid from thymus gland, spleen, kidney, pancreas and liver and the average respective yields from 10 lb. of gland were: thymus, 150.0 gm.; spleen, 40.0 gm.; kidney, 25.0 gm.; pancreas, 35.0 gm.; and liver, 18.0 gm. The hydrolysis of the nucleic acids for the purpose of estimating the purin bases was carried out in the same way as described previously by the author, with the exception that instead of absolute methyl alcohol, one containing 5% of water was employed. The nucleic acid (50 gm.) is suspended in 500 c.c. of 95% methyl alcohol and hydrogen chlorid gas is passed for 2 hours. The acid soon dissolves and gradually the hydrochlorids of the bases settle out. To complete the separation the reaction product is allowed to stand over night.

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**Microchemical Detection of Tryptophan in Plants.**

*Fritz Kretz, Biochem. Ztschr., Berlin, 130:86, June 20, 1922.*

Whereas completely decomposed casein, i. e. a mixture of all natural amino-acids, will maintain the nitrogen economy of an animal in equilibrium, equivalent casein deprived of but a single component—tryptophan—is no longer adequate for nutrition. A knowledge of the occurrence of tryptophan in vegetable albumin is therefore important for the appraisal of foodstuffs. In Voisenet's reaction, solutions containing tryptophan give a violet color upon addition of an excess of concentrated HCl and traces of formaldehyd and sodium nitrite. In order to make tryptophan detectable locally in tissue, Voisenet's method was elaborated as follows: After saturation of the test material with sodium silicate, the silicic acid is precipitated colloiddally by the concentrated HCl of the reagent, which gives a physical protection against destruction of the tissue structure by formation of a perfectly transparent membrane. In combination with albumin precipitation, the method was also applicable to the investigation of cytologic details in highly concentrated HCl. By this method tryptophan was detected in a mold fungus (*Boletus edulis*), in an alga and in some cormophytes. In higher plants high tryptophan content was found in the embryonic tissues while it was not detectable in primary or cutaneous tissue. Of permanent tissues, stored tissue and the conducting elements of the vascular bundles show abundant tryptophan. Tryptophan also occurs in all albuminous cell structures, such as the nucleus, nucleolus, protoplasm, aleurone, in albumin crystals and in the chloroplast stroma.

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**The Proteins of the Lima Bean, *Phaseolus Lunatus*.**

*D. B. Jones, C. E. F. Gersdorff, C. O. Johns and A. J. Finks, J. Biol. Chem., 53:231, Aug., 1922.*

The meal used for the preparation of the proteins was obtained from beans of 2 varieties, the "Fordhook bush" and "Carpenteria pole," which were obtained in the open market. No differences were observed in the results obtained from these 2 varieties. Two globulins

were isolated by fractional precipitation of sodium chlorid extracts by means of ammonium sulphate. The a-globulin was precipitated by addition of ammonium sulphate until the original extract was 0.25 saturated. The b-globulin separated between 0.45 and 0.75 saturation. A small fraction intermediate between the a-globulins and b-globulins, which consisted of a mixture of the 2 globulins, was removed and discarded. An albumin amounting to 1.75% of the meal was obtained from distilled water extracts of the bean meal after the globulins had been removed. Elementary analyses of the 3 proteins isolated, and determination of the basic amino-acids by the Van Slyke method, showed in general the same differences that were found between the corresponding proteins obtained from other beans which the authors studied. Both globulins and the albumin gave positive tests for tryptophan.

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#### **The Rate of Hydrolysis of Wheat Gliadin.**

*Hubert Bradford Vickery, J. Biol. Chem., 53: 495, Aug., 1922.*

Gliadin was selected for these experiments because it can be readily obtained in a state of purity, it has been thoroughly investigated with regard to its amino-acid make-up, and moreover, it contains a larger proportion of amid nitrogen, glutaminic acid, and prolin than any other protein hitherto analyzed. The rate at which gliadin is hydrolyzed at boiling temperature by certain reagents was investigated: 0.027, 0.1, 0.2, 0.5, 1.0, 2.0, 4.0 n. hydrochloric acid; 20% hydrochloric acid; 0.2, 4.0 n. sulphuric acid; 0.2, 1.0 n. sodium hydroxid; 0.2 n. barium hydroxid. Vickery found that the liberation of ammonia from gliadin, presumably amid hydrolysis, is readily effected at boiling temperature by very dilute acid or alkali. The ammonia is set free with great rapidity by the stronger acid reagents. Alkalis hydrolyze gliadin more rapidly in the early stages of hydrolysis than equivalent concentrations of acids in respect to both amid and peptid bindings. By the use of varying concentrations of acid-hydrolyzing reagents a picture of the hydrolysis of gliadin has been obtained from the splitting of the first bonds to the completion of the reaction. Acid hydrolysis is therefore a continuous process proceeding from the first to the last without marked interruption, due to the existence of stable complexes, and is therefore clearly distinguished from enzymatic hydrolysis.

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#### **Phosphoric Esters of Some Substituted Glucoses and Their Rate of Hydrolysis.**

*P. A. Levene and G. M. Meyer, J. Biol. Chem., 53: 431, Aug., 1922.*

In this article the authors present a table containing the rates of hydrolysis of 9 phosphoric esters of substituted glucoses with special reference to the allocation of the phosphoric acid. Report is made of the experimental preparation of benzylidene mono-acetone glucose, from which 1,2-mono-acetone-6-phosphoric acid glucose and mono-acetone phosphoric acid glucose were derived. To obtain the former, 50 gm. mono-acetone glucose is heated with 300 c.c. benzaldehyd and 50 gm.

anhydrous sodium sulphate at 145° C. for 5 hours. The warm solution is filtered and most of the benzaldehyd distilled out. When the residue begins to gelatinize, it is poured into 1 liter ligroin. The oily mass crystallizes when stirred, the crude product is filtered and washed with cold dry ether, and a nearly pure white product obtained. To make 1,2-mono-acetone-6-phosphoric acid glucose, 20 gm. of the preceding substance is dissolved in 75 c.c. dry pyridin and cooled to —20° C. A solution of 10 gm. phosphorous oxychlorid in 25 c.c. pyridin is at once added. The reaction mixture does not go above 20° C., and crystals of pyridin hydrochlorid settle on cooling. After the addition of cold water and barium hydroxid the pyridin is distilled out, the residue neutralized and its filtrate again treated and filtered and finally concentrated to a syrup. The syrup is taken up in absolute alcohol, filtered, and barium salt precipitated in a large volume of dry ether. The substance analyzed for mono-acetone phosphoric acid glucose. To prepare mono-acetone phosphoric acid glucose from mono-acetone benzylidene glucose, 7.271 gm. of the barium salt of this substance is dissolved in water making a volume of 50 c.c. Of this 3 c.c. is put in glass tubes with 2.1 c.c. n. H<sub>2</sub>SO<sub>4</sub> and 0.9 c.c. water and sealed. The tubes are heated at 100° C. at varying intervals, the contents of each tube made up to 100 c.c. and the phosphorus in 40 c.c. portions determined.

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**Sulphuric Esters of Some Substituted Glucoses and Their Rate of Hydrolysis.**

*P. A. Levene and G. M. Meyer, J. Biol. Chem., 53: 437, Aug., 1922.*

It has already been demonstrated that all known glucoproteins are protein derivatives of complex substances which are essentially sulphuric acid esters of disaccharids. Individual esters of this group differ in their stability. In regard to the phosphoric esters of glucose, the authors demonstrated experimentally that their resistance is determined by the position of the phosphoric acid on the sugar molecule. These considerations led the authors to synthesize 2 sulphuric acid sugar derivatives, one from diacetone glucose and the other from 1,2-acetone-3-benzoyl glucose. The first should yield a substance with the sulphuric acid attached to carbon atom 3, the second to either carbon atom 5 or 6. In the present experiments sulphuryl chlorid was employed. It was found advantageous to add the solution of sulphuryl chlorid in chloroform to a pyridin solution of the sugar derivative cooled to —10° C., and to allow the temperature to rise to about 30° C. Regarding the rates of hydrolysis, it was found that the ester having the sulphuric acid in position 5 or 6 was more stable than the one having the acid in position 3.

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**Benzylidene-Ethyl-Chitosaminate and Benzylidene-Ethyl-Diazogluconate (Mannonate).**

*P. A. Levene, J. Biol. Chem., 53: 449, Aug., 1922.*

The author has previously shown that benzylidene-ethyl-chitosaminate hydrochlorid on cautious treatment with sodium nitrite is converted into the corresponding diazo derivative. In the present work



the diazo compound was hydrolyzed and the resulting hydroxy-acid identified. Furthermore, the diazo compound was converted into the bromo and chloro compounds and the chloro derivative again converted into a 2-amino-hexonic acid. On hydrolysis of the diazo derivative with dilute acetic acid the formation of only 1 derivative was observed; i. e. benzylidene-ethyl gluconate. This was identified in the form of saccharic acid. The bromo and chloro derivatives were prepared each with a constant melting point and constant specific rotation, showing that in each instance only 1 substance and not a pair of epimers had been formed. Regarding the direction of the rotation of carbon atom 2 in the derivatives of the diazo compound, the author observed that on hydrolysis of the compound with dilute acids a substance resulted in which the rotation of the carbon atom 2 was in the opposite direction from that of the carbon atom 2 of chitosaminic acid. On the other hand, in the bromo, chloro, and amino derivatives, the rotation of the carbon atom 2 was the same as in the original chitosaminic acid. Compounds prepared in the course of the author's work were: benzylidene-chitosaminic acid, benzylidene-ethyl-chitosaminate; benzylidene-acetone-ethyl-chitosaminate; benzylidene-1-ethyl-2,3-anhydrogluconate (mannonate), and benzylidene-ethyl-desoxygluconate (mannonate). The first 3 substances were obtained in the process of preparation of free benzylidene-ethyl-chitosaminate. The benzylidene-acetone-ethyl-chitosaminate was obtained accidentally when it was attempted to recrystallize benzylidene-ethyl-chitosaminate from acetone. Benzylidene-1-ethyl-2,3-anhydrogluconate (mannonate) is obtained almost instantly when an alcoholic solution of benzylidene-ethyl-chitosaminate is poured into aqueous ammonia and the solution cooled to 0° C.

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#### Acceleration of Fermentation.

*H. von Euler and S. Karlsson, Biochem. Ztschr., Berlin, 130: 550, July 20, 1922.*

Euler and Myrbäck attempted to estimate the amount of water-soluble biocatalyzers in yeast, on the one hand by withdrawing from dried yeast all soluble biocatalyzers by washing and, on the other, by determining with what amounts of these biocatalyzers the normal fermentative power of the dried preparation could be reduced by one-half. Fractionation of biocatalyzers by heating was also attempted. The accelerating fermentative action of yeast extract must not be attributed unconditionally to B-vitamins. Harden and Young showed that the coenzyme could be withdrawn from dried yeast by treatment with water and that such a yeast no longer attacks zymohexoses, but regains this capacity upon addition of the washings containing the previously withdrawn coenzyme. Beuberg found that washed yeast of the aforesaid inactivity decomposes keto-acids, particularly pyroracemic acid, into acetaldehyde and carbonic acid. Thus the activity of at least one important constituent of zymase not containing coenzyme can be determined with quantitative exactitude by means of pyroracemic acid. The action of carboxylase is not materially affected by the presence of coenzyme. A comparison is, therefore, possible and the reaction constants can be specified for pyroracemic acid cleavage as well as for

glucose fermentation. So far it has not been possible to find a substitute for the coenzyme in a substance derived from animal or vegetable material and belonging to the vitamins. On the contrary, a certain amount of the coenzyme must be added in order to effect further activation by a vitamin. Thus, the biocatalyzers include substances that render dried yeast, which is in itself active only toward keto-acids, active also toward hexoses; those of unknown composition from juices, cells or tissues which effect zymohexose fermentation of washed yeasts only in the presence of coenzyme (representatives of the first group), as in wheat embryos and lemons, vitamin B of milk and serum, and familiar activators like zymophosphate or salts of organic acids. In the case of dried bottom yeast, the coenzyme is easily extracted completely by water so that the fermentative activity of the residue corresponds at most to the yeast's spontaneous fermentation. With top yeast, such extraction is not possible. Finally, juices and extracts possessing strong vitamin B action do not activate washed dried yeast without coenzyme, but in the latter's presence fermentation is strongly accelerated.

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**The Action of Mercury Bichlorid, Phenol and Quinin on Yeast.**

*Georg Joachimoglu, Biochem. Ztschr., Berlin, 130:239, June 20, 1922.*

Various experimental pharmacologic and physiologic results (for instance Pflüger's law) have been enlisted as proof of Arndt-Schulz's so-called biologic law that small amounts of a poison act inversely to large amounts, the former exciting, the latter paralyzing. The experimental foundations of this law are due chiefly to Hugo Schulz, who found that mercury bichlorid and other poisons (iodin, bromin, arsenous acid, chromic acid, salicylic acid, formic acid) in weak concentrations (mercuric chlorid 1:500,000 to 1:700,000) increase the activity of yeast considerably as compared with untreated controls. In this not the evolved carbon dioxid, but the pressure exerted by its evolution was measured with a mercurial manometer. The tabulated figures indicate the distances in centimeters covered by the mercurial columns within 15 min. Subsequently Schulz described an apparatus for the graphic registration of fermentative processes. The construction of a similar apparatus has been attempted frequently without satisfactory results. With all forms it is essential to bear in mind that rubber tubes are not quite impervious to carbon dioxid. Apart from this Schulz considers it necessary to take into consideration when measuring the pressure exerted by the evolved carbon dioxid, that the amount of dissolved carbon dioxid in the fluid increases in proportion to the increasing pressure. But as pressure varies in the different preparations the amount of dissolved carbon dioxid also varies. By this is not meant that the method employed by Schulz is faulty. However, the great importance assigned to his experiments and the far-reaching conclusions drawn from them seemed to necessitate their reëxamination. In a previous investigation the author was unable to confirm Schulz's results respecting arsenous acid. Schulz states that

concentration of 1:400,000  $\text{As}_2\text{O}_3$  stimulates yeast to increased production of carbon dioxide but the author was unable to observe this action with similar concentrations. Experiments were therefore undertaken with mercury bichlorid, phenol and quinin as regards their influence on fermentation in Buchner's flasks. The concentrations employed were mercury bichlorid 1:50,000 to 1:200,000, phenol 1:1000 to 1:10,000, and quinin hydrochlorid 1:360 to 1:5000. Neither these solutions nor arsenous acid accelerated fermentation in weak concentration. In the case of strychnin Arndt-Schulz's law does apply, but the exceptions are too numerous to warrant the assumption of an Arndt-Schulz law.

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**A Simple Appliance for the Automatic Registration of Yeast Fermentation.**

*Ernst Sieburg, Biochem. Ztschr., Berlin, 130:459, July 20, 1922.*

Only the final process, the evolution of carbon dioxide, is dealt with. Instead of complicated apparatus, the author employs a kymograph adjustable to a slow reaction and several U-shaped glass tubes with open arms of different lengths. The internal diameter is about 11 mm. so that a fluid 1 cm. in height corresponds to a volume of 1 c.c. The length of the shorter arm up to the bend is about 13 cm., that of the longer one about 18 cm. The tube receives 10 c.c. mercury, and the shorter arm, 5 c.c. sugar solution containing a yeast suspension. The arm is inclined in such a manner that the fluid almost reaches the opening and is closed with a rubber stopper so that very little or no air remains. In the longer tube, resting on the mercury, is a cone-shaped sealing-wax float. In its point is inserted a metal wire, as inelastic as possible, in the upper end of which is a straw to serve as recorder. This is connected, by means of a piece of cork, at right angles to the wire. In order to avoid considerable excursions of the registering lever from concussions, the longer arm is closed with a cork plate containing a central opening for the wire to pass through without appreciable friction. Two or three tubes, thus fitted and fixed on a stand, are placed in a water-bath at definite temperature. The points of the recorders are placed against the blackened drum of the kymograph at equal intervals vertically above each other and are gently pressed against the drum by a plummet.

The curves vary in accordance with the properties of the yeast employed and with the temperature, both as regards the latent period previous to the rise and the steepness and height of the curves themselves. The steepness is an expression of the velocity; the height, an expression of the quantitative course of the process. The tube in which the smallest volume of gas is expected should record lowest on the registration surface. This apparatus permits comparative demonstrations of the fermentative activity of different kinds of yeast with the same substrate; the fermenting velocities of different varieties of sugar with the use of a definite yeast species; the influence (acceleration or retardation) of different substances on the fermentative process, and the course of fermentation in the presence of yeast poisons in different dilutions.

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**The Synthesis of Fats (Glycerids).**

*C. Amberger and K. Bromig, Biochem. Ztschr., Berlin, 130:252, June 20, 1922.*

Synthetic glycerids were compared with those isolated from goose fat. The methods available for the synthesis of mixed triglycerids include (1) preparation of glycerids from halogen hydrins by heating with soap at high temperature (Grün); (2) preparation in accordance with researches of Fischer, Bergmann and Bärwind from iodohydrin or over acetone glycerin or acylacetone glycerin, and (3) preparation of asymmetric triglycerids from 2-phenol-5-methylol-oxazolidin. Fischer's method was employed for the syntheses. The original material was iodohydrin. On this the respective fatty acid chlorid was allowed to act and the di-fatty acid prepared from the  $\alpha\beta$ -fatty acid- $\alpha$ -iodohydrin by cleavage of the halogen with silver nitrate. Acetone glycerin was also used as original material. The various preparations were analyzed and their saponification number, molecular weight and melting point were determined. The synthesis of glycerids from diacyl halogen hydrin under the influence of fatty acids or sebatic salts at considerable temperature does not warrant conclusions regarding the position of the acid groups in the glycerid molecule. The prevalent assumption that the acyls already present in the molecule retain their position unchanged upon the introduction of new acid groups is not always correct. The steardipalmitin present in goose fat, with melting point  $63^{\circ}$  C. is an  $\alpha\beta$ -dipalmitin. The compound melting at  $57.7^{\circ}$  C. represents the isomerid  $\beta$ -stearo- $\alpha\alpha$ -dipalmitin. The palmitodistearin, melting point  $68^{\circ}$  C., detected in the fats, is not an  $\alpha$ -palmito- $\alpha\beta$ -distearin as hitherto assumed, but its isomerid,  $\beta$ -palmito- $\alpha\alpha$ -distearin. The palmitodistearin melting at  $63^{\circ}$  C. is not a  $\beta$ -palmito- $\alpha\beta$ -distearin, but its isomerid  $\alpha$ -palmito- $\alpha\beta$ -distearin. The synthesis of palmitodiolein over acetone glycerin leads to the desired results while in the preparation of  $\alpha$ -oleodistearin from  $\alpha$ -monoölein and stearic acid chlorid, oleodistearin is probably obtained. However, preponderant amounts of secondary reaction products are formed. The synthesis of  $\beta$ -oleo- $\alpha\alpha$ -distearin from  $\alpha$ -iodohydrin by Fischer and Bergmann's method did not furnish satisfactory results. The yield of glycerids prepared by this method was always good while former syntheses from halogen hydrin and sebatic salts gave a poor yield and nonuniform substances. Simultaneous production of secondary products and isomeric glycerids was demonstrated.

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**Precipitation Reactions in Solutions of Chlorophyl and Other Pigments.**

*M. Eisler and L. Portheim, Biochem. Ztschr., Berlin, 130:497, July 20, 1922.*

If 2 boiled extracts obtained from various vegetable organs by the same extracting agent are mixed, no clouding and no precipitate are produced. This occurs only when a definite amount of an alcoholic extract of the green leaves of the same plant species is added to the

aqueous extract of an organ. It was found that the extracts could be precipitated more easily after standing 24 hours in the dark cooling chamber and that the alcohol content influenced clouding. The occurrence of the reaction in floral extracts at first manifested itself by the appearance of a yellowish tinge and the clouding of the clear, blue-green chlorophyll solution until, finally, increasingly large flakes were precipitated, partly decolorizing the liquid. But the reaction did not occur either with distilled water alone or with alcohol, so that the precipitation reaction depends on a mutual influence of the leaf extract and the water-soluble extractives from flowers. In this albuminous substances and salts may be concerned. Experiments with vegetable organs rich in albumin, such as cotyledons of *Phaseolus*, confirm this. The same alteration was, however, caused by animal protein substances (horse serum in 1:10,000 dilution). In themselves no longer capable of precipitating chlorophyll, they were able to protect it against alteration by water.

Coagulable albumin has the strongest effects, which are observed with albumoses and bouillon-peptones, very slightly with pure peptone and not at all with lower decomposition products. In the authors' mixture only the chlorophyll can be considered capable of reacting, because lipoids rich in albumin are present in the leaf extracts in such small amounts that a carrying down of the chlorophyll is inconceivable. As green leaves contain carotin in addition to xanthophyll, an alcoholic extract of the root of *Daucus carota* yielded the same result. Crude chlorophyll and all its constituents react similarly. When colorless parts of parti-colored leaves were employed no precipitation occurred. Owing to the similarity between blood pigment and leaf pigment, the behavior of hematoporphyrin was noteworthy; it was not precipitated by serum-albumin. Other pigments were also investigated; anthocyanin from red cabbage caused immediate clouding of the extract upon addition of horse serum. Pigments of *Bacillus prodigiosus* and *Bacillus violaceus* gave a negative result. In alcoholic extracts the pigments, in aqueous ones the albuminous substances were concerned in the production of the reaction.

Precipitation can take place only when the chlorophyll particles of lessened dispersity and albumin enter into adsorptive combination. Solubility also depends on chlorophyll concentration, while, on the other hand, sufficient albumin for precipitation must be present. The precipitate in the alcoholic leaf extract produced by albumin addition contains the green and yellow constituents of chlorophyll. Addition of water causes a yellow discoloration of the chlorophyll extracts. They are yellowish green by transmitted light, green by reflected light. The passage of a strong ray of light shows no fluorescence, which latter is observed when the colloidal chlorophyll solutions are placed in front of Reichert's fluorescence apparatus.

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#### The Water-Soluble Constituents of the Alfalfa Plant.

*Thomas B. Osborne, Alfred J. Wakeman and Charles S. Leavenworth, J. Biol. Chem., 53:411, Aug., 1922.*

Observations were made respecting some of the chemical constituents of chlorophyll-free juice obtained from the alfalfa plant by a  
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method the authors have previously described. In a particular lot of alfalfa 36.9% of the dry solids, 41.6% of the nitrogen, and 69.3% of the inorganic matter were found to be soluble in water. Analysis of the ash of alfalfa juice fractions, showed that the inorganic constituents were: Ca, Mg, Na, K, Fe,  $\text{PO}_4$ ,  $\text{SO}_4$ ,  $\text{SiO}_2$ ,  $\text{CO}_2$ , and Cl. The close agreement between the sum of these constituents and the 79.39 gm. calculated from direct determinations of the ash of the solids of the original juice, indicates that these analyses fairly represent their true composition.

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**The Influence of Selenium on Constructive and Energy Metabolism in the Plant in the Presence of the Radio-Activity of Air and Soil.**

*Julius Stoklasa, Biochem. Ztschr., Berlin, 130:604, July 20, 1922.*

Selenium is nearly always found in iron pyrites employed for the manufacture of sulphuric acid and in radio-active minerals. The leaves of plants growing in the vicinity of the burning pit-heaps of the north-western Bohemian coal mines show a peculiar yellowish-red color. From the biochemic standpoint the selenium which is eliminated in the form of granules in the palisade cells merits great attention inasmuch as selenium oxid is extremely toxic. Added selenium is oxidized to selenic acid by biochemic processes and the small quantities in which this is found might stimulate the formation of new living plant substance, as has been demonstrated experimentally. A comparatively large accumulation of selenium or selenic acid may occur in a soil manured abundantly with superphosphate and ammonium sulphate. Selenium and sulphur are wholly analogous. There is no more injurious factor in plant growth than iron sulphid in the form of iron pyrites (marcasite), which occurs as one of the most widely distributed deposits in bog formations in soils under rock. In weathering, oxidation and absorption of water lead to formation of ferrous sulphate and free sulphuric acid.

Selenium has actually been found in the root system and leaves of plants. Its action on the building up of new living substance in *Azotobacter* in presence and absence of radium emanation was investigated; also the influence of selenium on the development of plants under like conditions. The formation of new living bacterial substance was diminished considerably by selenium in the case of *Azotobacter chroococcum* which absorbs elementary nitrogen and utilizes the same for tissue building. In the germinative experiments radio-activity paralyzed the toxic action of selenium, which was observed partly also with *Azotobacter*. The seeds' germinative capacity and germinative energy were promoted by radio-activity. But in experiments in a dark room the toxic effects were not entirely abolished. Selenium, especially in the gaseous state in the form of dioxid, has a strong toxic action on protoplasm and on the plant cell's chlorophyl, much more so than sulphur dioxid. The toxicity acts too rapidly and acutely to enable radium emanation to exert a favorable influence. Interesting intoxication experiments were made in winter with selenites and selenates in which the photochemic reductions were less energetic than in summer. Experiments with strong and weak dosages showed selenium to have

been very slightly reduced in the leaf organ. Colloidal selenium was detectable in the intercellular spaces in very small amounts. These reductions were in marked contrast to those in which photochemic reduction took place with energetic solar radiation. During exposure selenium is converted into a form conducting electricity well, but in the dark into one that is a bad conductor. The selenium cell undergoes an alteration in the sense that another selenium modification is formed which is a good conductor of the electric current. It remains to be elucidated whether the action of radium rays may not bring about a cleavability of the atoms or a transformation of selenium into an allotropic form. Photosynthesis in the cell containing chlorophyll represents an endothermic process in which the potassium bicarbonate that is formed is decomposed, under the influence of light, radioactivity and probably also of selenium, into formic acid, oxygen and potassium carbonate, while the formic acid produced is converted into formaldehyd and oxygen. ,

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**The Estimation of the Total Nitrogen of the Urine and of the Residual Nitrogen of the Blood without Distillation and Titration.**

*Autenrieth and Taege, Münch. med. Wschnschr., 69:1141, Aug. 4, 1922.*

The total nitrogen of the urine as well as the residual nitrogen of the whole blood or serum can be determined with great accuracy by direct colorimetry with the aid of Nessler's test, after a previous mineralization of the organic substances according to the Kjeldahl technic with the use of cerium dioxid as a catalyzer; a distilling of the ammonia formed by the Kjeldahl technic is not necessary. Of the various substances which the authors tested for their catalytic action, cerium dioxid was found the most useful. The use of acetone-free methyl alcohol as advised by Folin has rendered good service to the authors in the removal of the albumin from the blood and the serum for the purpose of estimating the residual nitrogen. The proposed colorimetric method is much simpler to use than the formerly generally employed method; it needs neither to be distilled nor titrated. Another fact to be considered is that in practice, the 0.2 n. or the 0.1 n. solutions necessary for the titration are too often procured from dealers in chemicals and are very rarely examined as to their accuracy. But if the titer of such solutions is not determined and they are considered as normal solutions without examination, all the determinations made with them are incorrect. Mistakes are also made too often in the use of the indicator.

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**The Estimation of Urea in Urine by Friedländer's Method.**

*Carlo Alessandri, Riforma med., Naples, 38:699, July 24, 1922.*

Friedländer's method is founded upon the formation of a compound between the urea and mercury bichlorid, which is obtained under the aspect of a white precipitate in an ambient of sodium carbonate. The indication that the compound is completely formed is furnished

by the formation of a yellow-red-brownish precipitate of basic carbonate of mercury obtained through the gradual union of the excess mercuric bichlorid and the sodium carbonate of the ambient.

Having made experiments with this method with titered solutions of urea and having compared the results with those of the classic hypobromite method, the author holds that the temperature, the criterion of the valuation of the color of the precipitate, the slight sensibility of the indicating liquid and its tendency to become easily exhausted, constitute no slight causes of error. The different acidity of urines may also have some influence in the quantitative determination of the urea, since the reaction occurs more or less rapidly and the number of cubic centimeters of bichlorid may be greater or less than the number necessary, with an evident resultant error in calculation. The author, therefore, feels able to assert that Friedländer's method can render only an approximate service in the estimation of urea and, even so, calls for an experienced hand, to avoid the multiple causes of error above indicated.

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**The Behavior of Uric Acid in Solutions of Albumin.**

*Ludwig Pincussen, Klin. Wchnschr., Berlin, 1: 1462, July 15, 1922.*

If a certain amount of uric acid dissolved in a solution of lithium carbonate is added to a solution of egg albumin, analysis will reveal only a small amount of the uric acid: the greatest part has become coagulated with the precipitation of the albumin. If such a solution is digested antiseptically by the addition of a suitable phosphate mixture with trypsin in an incubator, an increasing (up to the total) amount of uric acid can be demonstrated. Digestion with pepsin in an acid reaction also shows a growing increase of the free uric acid. But if an albuminous solution containing uric acid, diluted only with sodium chlorid solution is digested with trypsin and without any buffer solution, a decrease of uric acid results, just as when an albumin-uric acid mixture is kept for a longer time at incubator temperature without the addition of ferment. If a serum-uric acid mixture is left to digest with trypsin in an incubator, the amount of the uric acid either remains constant or it is decreased, but most often there is an increase, especially with serum from icteric and nephritic patients. Opposite values are sometimes found in the rising or falling curves in the tested digestive mixtures taken at different times. These experiments show that the uric acid values of serum and other albuminous solutions obtained by the usual technic often do not represent true values.

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**A Note on the Determination of Uric Acid.**

*Henry Jackson, Jr., and Walter W. Palmer, J. Biol. Chem., 53: 373, Aug., 1922.*

The authors recently described in this journal a reagent which under given conditions would yield with uric acid a far greater color than was developed by the older Folin reagent. In this paper is described a simple method for the preparation of the reagent. The "B"

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salt is prepared as previously described. This dry solid is dissolved in 95% alcohol (about 250 c.c. alcohol for each 100 gm. of solid). A residue of simple phosphates remains undissolved. The solution is filtered and evaporated to dryness in a water-bath, with frequent decolorizations with bromin water. The dry product is dissolved in a little hot water, decolorized again, and evaporated once more to dryness. A 20% solution is now made of this purified "B" solid—accurate to about 1%. To each 100 c.c. of this solution are added 34 c.c. of an exactly 2.5% water solution of primary calcium phosphate (Baker analyzed C. P.). This final solution may now be used in the same manner as the more complicated reagent previously described.

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### **Comparative Acetone Determinations in Urine.**

*Kurt Käding, Biochem. Ztschr., Berlin, 130:448, July 20, 1922.*

For practical purposes, it is necessary to perform quantitative acetone determinations accurately, in the briefest manner, and without complicated apparatus. In man, acetone occurs principally in diabetes mellitus but may also be excreted by the urine from other causes in considerable amounts. Frommer and Emilewicz devised the salicylaldehyd test (acetone, in the presence of alkali hydrate, yields a red-colored condensation product with salicylaldehyd, bis-o-oxybenzalacetone). Engfeldt's modification is based on the precipitation of an orange to red crystalline mass from the cooled mixture. The author's experiments employed 4-fold diluted urine. To 0.25 l. of the mixture, 2 c.c. 25% sulphuric acid were added and the solution was then cooled on ice and distilled, distillation being completed in 20 min. No acetone was detectable in the residue. It is important to use ground-glass stoppers in distillation instead of rubber ones to prevent escape of acetone.

Schall employs the iron chlorid reaction in order to ascertain whether aceto-acetic acid is present. If much of the latter is present, the ammonia determination is to be carried out; if little, then aceto-acetic must be determined as such. The quantitative acetone determination is undertaken with a comparative solution of 2% acetone and 2 measures of 100 c.c. capacity each, which respectively receive the acetone and urine clarified with animal charcoal. Then follows treatment with sodium nitroprussid solution, caustic potash solution and glacial acetic acid; the measure containing the acetone solution is brought up to 50 c.c. with water; and water is added to the measure containing the urine until the solutions match in color by transmitted light. The height in the second measure multiplied by 0.04 denotes the acetone content. The more concentrated the caustic potash solution, the more permanent is the intensity of the red coloration. In Legal's test, aceto-acetic acid gives a color tone  $5\frac{1}{2}$  times as intense as with acetone. According to Schall, acetone can also be determined with Authenrieth's colorimeter. The ring test in the modification of Lieben's test (formation of iodin with Lugol's solution and alkali) is of importance as regards the time required for ring formation, which differs for the different substances (acetone, alcohol, lactic acid).

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**The Importance of Dimethylhydroresorcin in the Differentiation of Volatile Aldehyds in Body Fluids. Identification of Formaldehyd in Urine after Administration of Urotropin.**

*Wilhelm Stepp, Biochem. Ztschr., Berlin, 130: 578, July 20, 1922.*

Vorländer discovered the property of dimethylhydroresorcin of reacting to simple aldehyds with formation of well-crystallized condensation products. That enabled acetaldehyd to be isolated and identified. In a case of secondary contracted kidney in which urinary acetaldehyd was determined quantitatively each day, a sudden twenty-fold to thirty-fold increase of the normal values was observed. This condition was at first referred to the progressive uremic symptoms to which the patient succumbed. But the determination of the melting point of the crystals, obtained by condensing the aldehyd with dimedon, showed that one was not dealing with acetaldehyd at all. The melting point in reality points to formaldehyd. Subsequently it was established that the patient had accidentally received urotropin from which the formaldehyd was derived. It is desirable, therefore, when investigating volatile aldehyds to establish their nature by the preparation of strongly characterized derivatives, preferably in the form of condensation products with dimedon. Formaldehyd may be easily and certainly detected in body fluids with dimethylhydroresorcin.

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**The Effect of Water Ingestion on the Reducing Substances in the Blood and Urine.**

*A. Noorgaard, Biochem. Ztschr., Berlin, 130: 304, June 20, 1922.*

While the rise of micromethods for chemical determinations in blood and urine instigated numerous researches on the increase of blood sugar following ingestion of carbohydrates, the intake of water and its influence on the amount of reducing substances in blood and urine has found only scanty and mostly merely transitory discussion. The present research seeks to investigate the influence of water administration on the reducing capacity of blood and urine. This capacity was examined in an experimental person and the influence of water tested in the same. In the case of urine, the influence of water intake on diuresis, on the concentration of reducing substances and on the amount of reducing substances excreted in unit time were taken into consideration. Further, the proportion between the absolute amounts of excreted reducing substances in the urine and the concentration of these substances in the blood was ascertained. The following observations were made: If water diuresis be produced during deprivation, it is found that in some cases the blood's reducing capacity is slightly diminished. During increased diuresis the urine's reducing capacity falls far below that of the blood. The concentration of the urine's glucose content is, therefore, far below the blood's. The absolute amounts of excreted reducing substances are almost equal in unit time and are not influenced by diuresis. A certain proportion exists between the amount of reducing substances excreted in unit time and their simultaneous concentration in the blood, the excreted amounts being smaller with great reducing capacity of the blood.



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**The Adaptation of the Pentabromo-Acetone Method to the Quantitative Determination of Citric Acid in the Urine.**

*William B. McClure, J. Biol. Chem., 53:357, Aug., 1922.*

The determination of citric acid by the pentabromo-acetone method depends upon the formation of water-insoluble pentabromo-acetone, when citric acid is oxidized by potassium permanganate in the presence of bromin. Since, during the test for citric acid in the urine by the pentabromo-acetone method, bromin is liberated and sulphuric acid has been added previously, the conditions are present for the formation of the bromin precipitate. Should such precipitate be produced, at least a part of it would be present as an impurity in the pentabromo-acetone precipitate and would to that extent vitiate the results of the citric acid determination. In order to eliminate such an error, the author tried these procedures: (1) separation of the pentabromo-acetone from the bromin precipitate; (2) reduction of the amount of bromin precipitate formed; and (3) a combination of these 2 procedures. The author found that the pentabromo-acetone method may be used for the quantitative determination of citric acid in normal urine with satisfactory results if the unheated urine has been rendered alkaline, previously, by sodium hydroxid, and shaken with charcoal and filtered; and if the final precipitate is heated as a means of separating pentabromo-acetone from impurities.

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**Comparison of Pentabromacetone Method and Salant and Wise's Method for Citric Acid Determination in Urine.**

*Wm. B. McClure and L. W. Sauer, Am. J. Physiol., 62:140, Sept. 1, 1922.*

The authors found that where known quantities of sodium citrate were added to normal urine, the pentabromacetone method gave much better results than the method of Salant and Wise in 3 cases. In the fourth case the results by the 2 methods showed close comparison. McClure and Sauer believe that for quantitative work in urine the pentabromacetone method of citric acid determination is preferable.

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**The Determination of the Three Dissociation Constants of Citric Acid.**

*A. Baird Hastings and Donald D. Van Slyke, J. Biol. Chem., 53:269, Aug., 1922.*

The methods for the calculation of the dissociation constants of weak polybasic acids recently outlined by Van Slyke have been applied to citric acid. The values of the 3 constants have been found to be  $K'_1 = 8.3 \times 10^{-4}$ ,  $K'_2 = 4.1 \times 10^{-5}$ , and  $K'_3 = 3.2 \times 10^{-6}$ . The corresponding  $pK'$  values are 3.08, 4.39, and 5.49, respectively. The value of  $K'_1$ , agrees approximately with that of  $K_1$  found by other authors. The values of  $K'_2$  and  $K'_3$ , because of the overlapping effects of the carboxyl groups, have not been accessible by previous methods of calculation.

The article contains detailed tabulated, graphic and mathematical data.

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**The Chemistry of Homogentisinic Acid.**

*Carl T. Mörner, Upsala Läkaref. Förh., Stockholm, 27:77, No. 1-2, 1922.*

In 1912, Mörner published his first observations on this subject. The present communication is concerned with the behavior of homogentisinic acid on boiling with ferric chlorid. On the observance of certain simple precautions, homogentisinic acid (as well as its most closely related oxidation product, benzoquinon-acetic acid, which is not volatile by itself) gives, on boiling with a solution of ferric chlorid in excess, an easily crystallizable, volatile, chlorid-rich quinon substance which can be easily isolated from the distillate on account of its exceptionally great insolubility. Numerous and varied experiments have shown that, as a rule, the yield of quinon substance is greater from benzoquinon-acetic acid than from homogentisinic acid itself, although equimolecular quantities of the 2 have been used; an equal yield was obtained only after boiling with ferric chlorid. In one and the same kind of test, it was found that, the volume of the ferric chlorid solution being constant, the yield of quinon substance depended largely on the concentration of the ferric chlorid in the solution. Other conditions being the same, and the most suitable concentration of the ferric chlorid solution being the same, the yield of quinon substance seemed to depend largely on the volume of this solution. The concentration and volume of the ferric chlorid solution being constant, it was found that the yield of quinon substance depended largely on the quantity of the material to be tested. Ringing the changes on the 24 different combinations of the constituents of the reactions, Mörner found the most effective (in the case of homogentisinic acid) the distillation of 0.33 gm. (added after boiling had been started) with 400 c.c. of a 37.5% solution of ferric chlorid. A study has also been made of the physical properties of crystallized homogentisinic acid.

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(1b—146)

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**Bile-Pigments. XI. Technical Preparation of Bovine Gall-Stones and the Recovery and Purification of Bilirubin.**

*W. Küster, Hoppe Seyler's Ztschr. f. physiol. Chem., Berlin, 121:110, July 29, 1922.*

Some further experiences are communicated on the preparation of gall-stone powder and derivative substances, particularly bilirubin and its modifications, as well as bilirubin-ammonium. The first ether extraction, completed in about 3 days with 150 gm. gall-stone powder, yields an extract that can be divided into a readily and slightly soluble fraction in a little ether at room temperature. The former is strongly colored and consists of fats and esters of cholesterol, while the latter is almost colorless and consists of a choleic acid. The extracts prepared

with boiling water contain salts of water-insoluble acids. After precipitating with dilute sulphuric acid a part is soluble in ether. In this too a bile acid is detectable. The largest amounts of substance from gall-stone powder are always extracted by 10% acetic acid, in which case an ether-soluble acid is sometimes met with. The second ethereal extraction yields a choleic acid soluble with difficulty in ether (from which desoxycholic acid is obtained by recrystallization from glacial acetic acid) and a mixture readily soluble in ether (from which stearic acid was isolated). It has not been possible so far to prepare a characteristic substance from the mixture insoluble in petroleum ether, nor to break up into definable substances the mixture extractable from gall-stones with boiling alcohol. Bilirubin derivatives are certainly contained in it. It would be important to demonstrate the existence of intermediate products between the blood-pigment of the prosthetic group and bilirubin, or between bilirubin and bilihumin. With chloroform the first exhaustive extraction yields an orange crude bilirubin containing chlorin and sulphur. On treating the residual gall-stone powder with 10% acetic acid, ether and alcohol, red-brown bilirubin is formed. The former is then converted into bilirubin-ammonium, which was tested by (1) solution in 10-15 parts slightly warmed pyridin, and (2) by action of 15 c.c. boiling alcohol on 2.5 gm. bilirubin-ammonium. Bilirubin was also prepared directly from gall-stone powder without chloroform extraction. After extraction of the bilirubin there remain in the mother fluid parts of the gall-stone powder which are readily soluble in chloroform and precipitable by alcohol. This is a greenish bilirubin which is then extracted with cold pyridin. After distillation there remains a red bilirubin and on the margin also long yellow needles, probably mesobilirubin. Reihling stated that hematinic acid is formed in the oxidation of choleprasin. The reëxamination showed that this substance is accompanied by bilirubin derivatives which yield hematinic acid on oxidation. Choleprasin is merely a derivative of globin.

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**Bile-Pigments. XII. The Action of Diazomethane on Bilirubin and Biliverdin, the Oxidation of Bilirubin in Alkaline Reaction and the Action of Hydrogen Bromid-Glacial Acetic Acid on Bilirubin.**

*W. Küster, Hoppe Seyler's Ztschr. f. physiol. Chem., Berlin, 121:94, July 29, 1922.*

The action of diazomethane on bilirubin produces, besides dimethylation, an addition of diazomethane. It was sought to obtain dimethylation alone, as it had been observed that a part of the bilirubin was dissolved during the action of diazomethane, though a part was again precipitated on standing. The filtrates obtained in the estimation of the basicity of bilirubin were subjected to atmospheric oxidation in the ice-chest at 4-7° C. in shallow dishes. Small amounts of a brown substance appeared 10 hours after filtration and 4-5 days later distinct separation of orange bilirubin occurred, the solution showing a greenish tinge. Eight days later a portion was filtered, whereupon only orange bilirubin precipitated. Twenty days later the solution had a pure

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green color. Following acidification, filtration and drying, 3.2 gm. biliverdin were obtained from 4.6 gm. bilirubin. The greater part of the loss was due certainly to the bilirubin precipitated during oxidation. Addition of more alkali during oxidation would have avoided the losses, as biliverdin consumes more alkali than does bilirubin. The biliverdin was insoluble in ether and chloroform, but soluble in alcohols. Esterification of biliverdin with diazomethane yielded black, not pronounced crystalline substances dissolving with a green color in alcohols, benzol and acetone. The occurrence of hematinic acid was demonstrated in the action of alkalines on bilirubin and in the latter's oxidation in alkaline solution. A further interference in the bilirubin molecule, which disclosed structural differences compared to the porphyrins, consisted in the action of hydrogen bromid-glacial acetic acid. It was shown that bilirubin contains 3 unsatisfied parts in relation to hydrogen bromid but only the 1 part not present in hemin is capable of adding the reagent and of combining bromin firmly. At the other 2 parts a loose fixation of hydrogen bromid occurs.

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### **Bile-Pigments. XIII. Hexachlororubilinic Acid.**

*W. Küster and W. Hermann, Hoppe Seyler's Ztschr. f. physiol. Chem., Berlin, 121:110, July 29, 1922.*

The parts of the prosthetic group of the blood-pigment which add hydrogen bromid in the conversion into hematoporphyrin no longer have, in bilirubin, the arrangement qualifying for the absorption of hydrogen bromid. But there is another grouping from which it must be possible to produce the methylethylmaleic acid imid by reduction with sodium amalgam and subsequent oxidation. The present research seeks to explain the grouping of the carboxyl-containing pyrrol nuclei of bilirubin and also the different behavior of bilirubin and porphyrin. The bilirubin molecule is split by nascent chlorin, a binuclear pyrrol derivative or dibasic acid being obtained which may be designated as rubilinic acid. This is obtained in the form of a chlorin substitution product, for which the name hexachlororubilinic acid is proposed, in conformity with the number of chlorin atoms. In the course of this oxidative decomposition no hematinic acid is produced. Hexachlororubilinic acid is prepared by rubbing 1 gm. orange bilirubin with 40 c.c. glacial acetic acid to a fine suspension and adding 45 c.c. hydrochloric acid with 1 c.c. perhydrol (Merck). With warming, solution of the bilirubin sets in, the color changing through green, blue and violet to deep red. After filtering, 1 c.c. perhydrol is added, after which the solution brightens within an hour. This is precipitated in 200 c.c. water, yielding a white flocculent precipitate which is washed and dried. After further procedures the acid is obtained in the form of a bright yellow powder consisting of small rounded particles. In order to demonstrate the dibasicity, esterification experiments were carried out with the result that addition of hydrochloric acid at room temperature to the methyl alcoholic solution effected only monomethylation, while dimethylation was achieved at water-bath temperature. The acid could not be acetylated and tests for the presence of a carbonyl were unsuccessful.

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### Some Pyrrol Derivatives.

*W. Küster, Hoppe Seyler's Ztschr. f. physiol. Chem., Berlin, 121: 135, July 29, 1922.*

In the course of investigations on the synthesis of hematinic acid and on the constitution of the prosthetic group of blood-pigments or bile-pigments some new pyrrol derivatives were discovered. These include 2,4-dimethylpyrrol-3,5-dicarboxylic acid ethylester, 2,4-dimethylpyrroldicarboxylic acid-3-ethyl-5-methylester, 2,4-dimethylpyrroldicarboxylic acid-3 methyl-5 ethylester, and 2,4-dimethyl-e-carboxymethylpyrrol-5-carboxylic acid. The first derivative was obtained from acetoacetic acid methylester, the second from the same, 12 gm. being dissolved in 150 c.c. glacial acetic acid and introduced into an ice-cold aqueous solution of 7.5 gm. sodium nitrite. Then followed addition of 13 gm. acetoacetic acid ethylester and reduction of the mixture with 100 gm. zinc dust. The third ester was obtained in acetic solution from 6.5 gm. isonitroacetoacetic ethylester and 5.8 gm. acetoacetic acid methylester. In the case of the acids the ester was saponified with 10% lye in 96% alcohol. Mention should also be made of 2,4 dimethyl-e-carboxethylpyrrol-5-azobenzolsulphonic acid, 2,4-2',4'-tetramethyl-3,3'-dicarboxethylpyrocoll, 2,4-dimethyl-e-carboxethylpyrrol. Thereupon from the pyrrol (by solution in 10 c.c. absolute alcohol and employing 0.8 gm. pyrrol and adding 0.9 gm. diazobenzolsulphonic acid in aqueous solution) 2,4 dimethyl-3-carboxymethylpyrrol-5-azobenzolsulphonic acid, bis-(2,4-dimethyl-3-carboxethylpyrrol)-methane, bis-(2,4 dimethyl-3-carboxethylpyrryl)-methane hydrochlorid, bis-(2,4 dimethyl-3-carboxethylpyrryl)-nitrophenyl methane, bis-(2,4 dimethyl-3-carboxethylpyrryl)-furyl-methane. Further, there were prepared methylcarboxethyl maleic imid under the action of chromic acid, 2,5-dimethyl-3-carboxethylpyrrol-4-methyl chlorid from pyrrol and methyl chlorid ether, both dissolved in ether in the form of a reddish (solidifying and then liquefying) oil. Finally may be mentioned 3-oxy-5-methyl-4-carboxethylpyrrolenyl-3-p-methoxyphenyl methane, 3-oxy-5-methyl-4-carboxethylpyrrol, 2-acetyl-3-acetoxy-5-methyl-4-carboxethylpyrrol, 2-isopropyliden-3-oxy-5-methyl-4-carboxethylpyrrolenin, 2,4 dimethyl-4-acetyl-3-carboxethylpyrrol, 2,4-dimethyl-5-acetyl-4-nitrosopyrrol, 2,4 dimethyl-5-acetylpyrrol-3-azobenzolsulphonic acid, 2,4 dimethyl-5-acetylpyrrol-3-azonaphthalinsulphonic acid and 3,5 diacetic acid pyrrol-2,4-dicarboxylic acid tetramethylester.

## 1c. PHARMACOLOGY AND TOXICOLOGY

(1c—90)

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**The Relation between the Chemical Constitution and Physiologic Action of Organic Compounds.**

*A. Oswald, Rev. méd. de la Suisse Rom., Lausanne, 42: 481, Aug., 1922.*

Drug actions may be more or less simplified by remembering that certain radicles possess certain characters which appear in analogous



compounds containing these radicles. For instance, the phenyl radicle ( $C_6H_5$ ) is antipyretic, and the analogous compounds of the anilin derivatives, phenol derivatives, pyrazolon derivatives and hydrazin derivatives are also antipyretic. Among these groups are included acetanilid, salicylic acid, antipyrin, pyrocin, etc. Reactions occurring in vitro are not the same as those manifested in vivo, because the latter occur in a colloid medium, which modifies the reactions. Moreover, many colloids are present. They modify the speed, but not the quality, of the reactions, the physiologic action depending on the quality of the chemical changes. The latter, affected physically or physicochemically, may be hastened, retarded or prevented. Notwithstanding our ignorance, in many cases, of the conditions required to guarantee a given physiologic action, it is generally true that various physiologic effects may be reduced to a few types. The 3 primary organic compounds are methane, benzene and ammonia, whose corresponding essential properties are aliphatic, aromatic and nitrogenous. Aliphatic substances paralyze protoplasm, especially of the central nervous system, diminishing sensation. They include sedatives, narcotics and general anesthetics, and act in other familiar ways. The properties of aromatic and nitrogenous compounds are similarly typical. Inhibiting radicles may be introduced into compounds, modifying or abolishing the type-effect. The groups formed by various radicles are chromophore, narcophore, toxophore, etc.

Substances of one group may be combined with compounds of the same, or other groups. Molecular weight must be reckoned with. The physiologic action diminishes with the degree of saturation. Typical actions may be diminished or augmented. Secondary modifications and effects may be produced by introducing or withdrawing various radicles. The examples cited apply to all organic compounds. For substances whose composition is not exactly known, their physiologic action may be presumed, but not stated positively in advance.

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### **The Action of Drugs and the Toxin Sensitiveness of Cells and Tissues.**

*Handovsky, Klin. Wchnschr., Berlin, 1: 1541, July 29, 1922.*

The degree of action of a drug depends both on the toxicity of the substance and the toxin sensitiveness of the tissues. It is known that many individuals have an idiosyncrasy to certain toxins and also that there is an anaphylactic hypersensitiveness to protein-like substances which may be manifested even in individual organs and, therefore, indicates a sensitization of the body cells. Moreover, it is known that there are varying degrees of toxin sensitiveness in vagotonics and sympathicotomics to autonomous toxins, and that a changed toxin sensitiveness of the frog's heart takes place through artificial changes in nervous correlation; the dependence of toxin sensitiveness on the tonus of the musculature and the degree of stimulation of nerve centers is recognized. But as the condition of an organ and its toxin sensitiveness are very complex phenomena, the changes in the colloid condition of cell protoplasm and its effect on sensitiveness to different toxins

has been studied. Such changes concern the water content of the tissues, the degree of dispersibility (precipitation, adsorption, solidification, liquefaction) and disintegration.

There are several methods for the observation of the colloid condition of living cells: The determination of the volume of the cell gives a measure of its water content. The determination of the internal electric conductivity, ultramicroscopic examination, examination of the viscosity of the protoplasm and a study of the action of substances of known colloid chemical properties on the cells have shown that an increased gelatinization of the protoplasm decreases the toxin sensitivity of the cells.

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### **The Action of Drugs and Their Combinations on the Intracranial Vessels.**

*Joh. Kühn, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:74, July 28, 1922.*

Substances from the aromatic series were chiefly used; there is little accurate knowledge of their mode of action or of the nature of the headaches treated, but it is assumed that there is a vasomotor action on the blood-vessels of the head. Attempts were made to show whether combinations of the drugs caused a strengthening or a weakening or any other effect on the action of the individual drugs. The method of testing is that of Hürthle and is based on the fact that the lateral pressure is measured at 2 points on the artery of a region of the body, in order that, with varying heights of aortic pressure, a change in the innervation of the vessel may be recognized. The drugs used were salicylates (sodium salicylate), antipyrin, caffein and phenocoll hydrochlorid and combinations of them. It was found that each of them alone, as well as in combination with others, exercised a vasomotor action on the cerebral vessels, sometimes in the direction of dilatation, sometimes of constriction.

In different individuals, or sometimes in the same individual under different conditions, the effect is not always the same. Variations occur from the normal standard that one drug has a dilating and another a constricting action. Some had the effect of strengthening the action of others, provided the individual drugs acted in the same direction; if they had opposite actions, they did not neutralize each other but the effect in one or the other direction was brought out more strongly. Among 7 cases of injection of sodium salicylate, 6 patients showed dilatation of the cerebral vessels; and one, constriction immediately followed by marked dilatation. When caffein and phenocoll were used together, there was dilatation in 2 cases and constriction in 2; with antipyrin and caffein, dilatation in 4 cases and constriction in 1 followed by pronounced dilatation; with sodium salicylate and caffein, dilatation in 2 cases, constriction in 1; when sodium salicylate and antipyrin were used in 2 experimental animals, there was constriction in 2 cases followed by dilatation in 1 and no reaction; and when sodium salicylate and phenocoll were used together, there was dilatation in 2 cases and constriction in 2.

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**Pharmacognostic Notes. I. Chinese Materia Medica.**

*B. E. Read, China M. J., Shanghai, 36: 303, July, 1922.*

*Illicium anisatum* (*pa-chiao-hui-hsiang*).—The seeds of this plant are used for producing commercial anise oil. The colloquial name is Ta-liao. There are commonly sold at a cheaper rate the very poisonous seeds of *Anisatum religiosum*. Death from poisoning by these latter seeds is not an uncommon occurrence. The identity of the plant *Illicium religiosum* is fully established. Its poisonous principle, sikimin, is well-known and its convulsant effects have also been recorded; 3.5 gm. of these seeds administered to a cat in the laboratory produce violent convulsions and death in a few hours. A public campaign to prevent its collection, sale and use would be a great benefit. The best antidote for this poison is chloral hydrate, or spirits of chloroform diluted with water.

*Hydnocarpus anthelmintica* (*ta-feng-tzu*).—Stuart gives the seeds of this tree incorrectly as *Gynocardia odorator*. When compared with samples of genuine chaulmoogra seeds and different varieties of *Hydnocarpus* seeds brought to Peking from Indo-China, the author does not hesitate to pronounce the Chinese seeds as belonging to *Hydnocarpus anthelmintica*. It is of interest that Muir considers the esters of this oil to be of considerable value.

*Datura Alba, Datura Stramonium* (*man-t'o-lo*).—The Chinese do not distinguish between these 2 species. The latter has been found growing in great abundance in all parts of Chihli on low-lying ground and on hills over 3000 feet high. The leaves from Jehol have 16.21% ash and 0.149% of alkaloid. The seeds yield an average of 3.48% ash, 23.8% fixed oil and 1.49% of volatile oil. This plant grows on ash heaps outside of Chinese villages. Attempts to purchase man-t'o-lo in the large cities in the North have proved fruitless, probably because it is regarded as a very strong poison. Considering the close botanical, chemical and therapeutic nature of the several daturas it might be well to accept this name in China for stramonium.

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**The Nature of Astringent Action.**

*Franz Müller, Deutsch. med. Wchnschr., Leipsic, 48: 1097, Aug. 18, 1922.*

An astringent action is possessed by all substances which precipitate protein sols in an absolutely or almost absolutely insoluble form. Among these are tannic acids, the salts of the heavy metals, the calcium salts and numerous acids. The hydrogen ion also precipitates protein solutions. The aim of the use of astringents in wound treatment (S. Löwe and G. Magnus) is the precipitation of protein and the overcoming of injurious products of protein catabolism in the wound secretion, by which a precipitation of the bacteria is also brought about. By the artificial covering produced, which protects the surface, astringents often act more favorably than disinfectants. Increased density of the surface and irritation and corrosion in their varying combinations are hard to separate in the experiments (S. Löwe and O. Umlandt).

The tannic acids furnish a pure picture of an astringent action. In the action of the salts of the heavy metals, we see that the transition from an astringent to a corrosive action is a function of the ionized salt. This is shown experimentally in silver nitrate. Nor can a sharp boundary line be drawn between superficial tanning and corrosion and secondary irritation of the surrounding tissues.

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**The Pharmacology of Active Vegetable Galenical Preparations.**

*D. Manuel Alvarez Ude, Siglo méd., Madrid, 70: 106, 159, July 29, Aug. 12, 1922.*

Separation of active principles and modern synthetic preparations have led to a certain disuse of plant products, yet many are not so inert as supposed. Many substances have the power of enhancing drug effect, as shown by combining cochineal with cantharides. Certain whole plants are especially effective, such as Equisetum. Cascara is especially valuable because of the large number of methyloxanthraquinone substances which it contains. The same is true of a number of other plants containing these substances. Natural drugs may be more valuable than artificial ones, and merit thorough study. Derivatives of active substances may occur in entire plant-groups. New substances are being constantly discovered. Slavish following of innovations is not desirable. A tendency to revert to galenicals is now evident in England and the United States, the practice being toward rational and scientific combinations. The use of so-called specifics is often irrational and illusory. (*To be continued*)

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**The Influence of Small Amounts of Methyl Alcohol on Nitrogen Metabolism.**

*Konrad Rewiger, Ztschr. f. d. ges. exper. Med., Berlin, 28: 368, June 30, 1922.*

Dogs in nitrogen equilibrium or in partial or complete hunger received 1.5-2.5 c.c. methyl alcohol per kilo of body weight and a 10-fold amount of water through a stomach tube. The nitrogen balance became negative (determination in urine by Kjeldahl's method). When, however, the dogs were overfed on protein the negative nitrogen balance did not occur. Tame rats received 0.6 c.c. methyl alcohol, diluted with water, through the stomach tube. Toxic symptoms appeared, but nitrogen output was not increased.

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**Theory of the Retention and Excretion of Bromin Salts and the Halogen Content of the Organism.**

*Baur and Oppenheimer, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94: 1, July 28, 1922.*

The theory that the pharmacologic action of the bromin salts is connected with the lack of chlorin which appears on the administration

of bromin is not satisfactory. But at any rate there is a connection between administration of bromin and poverty of chlorin. The accumulation of bromin in the body as well as the removal of halogens from it after a single or after daily administration of salts can be determined arithmetically on the basis of the mutual action of chlorin and bromin. The proportion of bromin in the total halogen content of the organism during or after treatment is correspondingly variable. From this relation the total salt content must also be reckoned. Most of the organs of the body make no distinction (so far as their function is concerned), between sodium bromid and sodium chlorid, and either can be given without causing any disturbance of bodily activity. But the brain and possibly the nerves react by a functional change, which gives the basis for the therapeutic action of bromids. From this physiologic equivalence of the 2 halogens it must be assumed that there is a condition of balance in the total salt content. The distribution of bromin in the organism is uniform; there are no special depots where it accumulates. If the total number of the halogen molecules is constant, then the number of molecules excreted in a given time must equal the number taken in during that time. This is naturally true only in an adult with normal kidneys. But the excretion of bromin is never quite equal to the intake. A bromin balance or saturation of the organism can never occur if the chlorin and bromin are given daily in equal quantity. If no sodium chlorid is given with the bromin salt, the loss in chlorin content is at first very pronounced, then less so, and at the end is extraordinarily protracted. This also occurs inversely with bromin, that is, with sudden cessation of bromin administration the body does not become completely free of bromin, but finally the amount becomes too small to be demonstratable by the method of weighing. Thus after giving 18 gm. sodium bromid in  $4\frac{1}{2}$  days, bromin was found in the cerebrospinal fluid in 13 days, and in the urine in 35 days after only 1 gm. was given. The sodium chlorid content of an adult man is calculated at 160-220 gm. In order to calculate the total content, a single dose of bromin is given. The number of excreted sodium chlorid molecules multiplied by the number of administered sodium bromid molecules, and divided by the number of molecules of excreted sodium bromid, gives the number of sodium chlorid molecules in the organism. If it be assumed that the organism is in halogen balance at the beginning of treatment, and the proportion of chlorin to bromin in the urine corresponds to that in the organism, this gives the formula for improving the excretion of sodium chlorid or sodium bromid for every day of the bromid treatment. A formula can also be found for the decrease of the chlorid content with increase of bromin. Bromin retention is due to the increasing rise in excretion on salt-free diet and the rise in the proportion of bromin in the total amount of salt; after stopping the bromid treatment the latter is removed from the organism, however, without ever reaching the former zero point.

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**The Distribution of the Cinchona Alkaloids in the Mammalian Organism.**

*Eduard Boecker, Biochem. Ztschr., Berlin, 130:312, June 20, 1922.*

These investigations deal particularly with the question whether the amount of cinchona alkaloids taken up by individual organs from



the lymph stream bears a proportionate relation to the weights of the organs, or whether certain organs have a pronounced affinity for cinchona alkaloids. Guinea-pigs were given subcutaneous quinin injections and were killed 1-48 hours later. The special object was to determine the proportion of quinin in lungs to weight of lungs, as compared to quinin in liver to weight of liver, the proportion of which quotients, as it were, express the specific quinin content of these organs. The guinea-pig might probably show no essentially different behavior toward quinin than does man. In both some of the alkaloid, though possibly in different amount, is excreted in the urine and some is evidently destroyed in the organism. In both also the quinin content of the organs and tissues diminishes constantly in course of time after the administration. According to Cahn-Bronner subcutaneous injection leads to formation of depots in consequence of partial precipitation, the relative quantity in the depots manifestly depending on the concentration of the solution. While the portion of alkaloid remaining in solution enters the lymph stream rapidly, as in intravenous injection, the depots are apparently depleted very slowly under certain circumstances. Details of these processes are not well understood. The experiments show that the lungs contain more quinin than the liver in the proportion of 1.6-2.2:1. The lungs actually take up more alkaloid than corresponds to their proportion of the whole body weight. In analogous experiments with peroral administration of quinin and optochin, the lungs also took up a disproportionately high amount of both alkaloids.

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#### **Digitonin and Its Decomposition Products.**

*A. Windaus and K. Weil, Hoppe Seyler's Ztschr. f. physiol. Chem., Berlin, 121:62, July 29, 1922.*

Digitonin, a finely crystallized saponin from the seeds of *Digitalis purpurea*, is freed with difficulty from accessory glucosids. As it gradually decomposes on heating determination of its melting point is not possible. Rotatory action and analysis are not very characteristic. Microscopic examination is the most useful. Years after the discovery of crystallized digitonin, about 15% of gitonin is still found in the material. Another hitherto unknown saponin is contained in the raw material. The formula of digitonin is  $C_{55}H_{70}O_{29}$ . During cleavage 2 molecules of galactose and probably also 2 molecules of glucose are formed in addition to digitogenin. In the saponification of digitonin, pentoses and hexoses are produced. Kiliani obtained crystallized digitogenin by splitting digitonin with alcoholic hydrochloric acid; on heating with acetic anhydrid it yields a crystallized acetyl derivative. Its formula is  $C_{81}H_{50}O_8$ . On recrystallization from ether-petroleum ether fine needles are formed, which have a constant melting point of 139° C. The purity of digitogenin can be determined by its behavior with methylmagnesium iodid, not even traces of methane being produced, so that it no longer contains an hydroxyl group. If digitogenin is oxidized with chromic acid there is formed digitogenic acid,  $C_{26}H_{38}O_7$ , which yields a crystallized dimethylester and a diethylester, a crystallized monoöxim acid and possibly also an acetyl derivative. The melting point of the acid differs according to the

nature of the solvent employed for recrystallization. Methyl digitogenate prepared with diazomethane melts in the pure state at  $146^{\circ}$ . It contains no hydroxyl group. The 3 acids described by Kiliani (gitonic, desoxydigitogenic and hydrodigitoic acids) are identical with gitogenic acid,  $C_{26}H_{40}O_6$ . Further, there are digitoic acid and  $\beta$ -digitogenic acid,  $C_{26}H_{38}O_7$ . The latter is said to have the formula  $C_{28}H_{44}O_8$  but crystallizes with 1 molecule of water. On the other hand digitoic acid is a decomposition product,  $C_{27}H_{42}O_7$ .  $\beta$ -digitogenic acid is obtained from the mother liquors of digitogenic acid. Finally, oxydigitogenic acid,  $C_{26}H_{38}O_9$ , formed by careful oxidation of digitogenic acid with potassium permanganate, is a tribasic acid, the same as digitic acid,  $C_{26}H_{38}O_{10}$ , which is formed by oxidation of digitogenic acid, digitoic acid or oxydigitogenic acid with strongly alkaline potassium permanganate solution. Besides this another derivative, anhydrodigitic acid, is said to be obtainable; this is an unsaturated monoketodicarboxylic acid.

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**Experiments in Blood Coagulation on Oral Administration of Euphyllin.**

*Karl Addicks, Deutsch. Arch. f. klin. Med., Leipsic, 140:117, July 25, 1922.*

Nonnenbruch and Szyszka have found that euphyllin after intravenous injection (0.48)—as well as the similar combinations, ethylene diamin acetate and ethylene diamin hydrochlorate and piperazin—hastens coagulation and has a hemostatic action. On Curschmann's authorization the author has tested the action of euphyllin on oral administration. Doses of 0.1-0.2 gm. (tablets of 0.1 gm. each) hasten coagulation for 2-3 hours; doses of 0.3 and 0.4 gm. produce a further hastening, up to 75%, which lasts for 5-7 hours; but this phenomenon is followed by a slight inhibition of coagulation. If the drug is given again the next day it has no effect or causes a slight slowing of coagulation.

Nonnenbruch and Szyszka, in confirmation of the teaching with reference to the influence of the spleen on coagulation, found that euphyllin had no effect on blood coagulation in rabbits whose spleens had been removed. But Addicks found in a patient whose spleen had been removed several years previous the same atypical action as in normal individuals. Probably here the lymph glands had begun to act vicariously for the spleen. In hemorrhagic diathesis, also, euphyllin seems to further coagulation. It is of equal value with serum, salt, calcium preparations and gelatin, but on intravenous injection it is superior to these agents in duration and intensity of action. The coagulation time was determined in a drop of blood from the ball of the finger by drawing a fine glass rod through a drop placed on a dry slide in a damp room and noting the appearance of the first fibrin threads. The time of coagulation in the puncture wound was also observed.

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(1c—101)

**Muscle Tremor with Muscarin.**

*W. Heubner, Klin. Wchnschr., Berlin, I:1509, July 22, 1922.*

After injection of a very large dose of mushroom muscarin a cat had not only salivation and difficult breathing but a fascicula muscle

tremor, such as is the rule after physostigmin, that at first became stronger on the administration of atropin. This observation deserves special attention because of the strict limitation of the action of mushroom muscarin to the parasympathetic nerve-endings and the question of an innervation of striated muscle by autonomic, especially parasympathetic elements.

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(1c—102)

(1c—102)

**Notes on the Secretory Action of Nicotinic Acid-Methyl Ester Chloromethylate.**

*Katsumi Haramaki, Biochem. Ztschr., Berlin, 130:267, June 20, 1922.*

Loewy and Wolffenstein found that substances (cesol and neo-cesol) are formed by addition of methyl groups to nicotinic acid ester which possess the sialogogic and aperient action of arecalin but greatly diminished toxicity. With these derivatives the flow of gastric juice was strongly promoted and salivary secretion was also increased.

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(1c—103)

(1c—103)

**Comparative Researches on the Action of Some Saponins on Red Blood-Corpuscles and Trypanosomes.**

*Yoshitsune Wada, Biochem. Ztschr., Berlin, 130:299, June 20, 1922.*

The vegetable substances termed saponins show very different quantitative action on red blood-corpuscles. Saponins are known that have a hemolytic action even in dilutions of 1:1,000,000 or more, while others show no hemolytic action in dilutions of 1:10,000. As regards the action of saponins on animal microorganisms, particularly on protozoa, the literature contains no indications of the degree of activity of different saponins. Levaditi and Rosenbaum showed that paramecii suspend their movements immediately in a 1:10,000 saponin concentration and are destroyed and that in this case cholesterol abolishes the action on paramecii. Experiments were carried out to compare the hemolytic capacity of certain saponins with their action on trypanosomes. For this purpose saponin, cyclamin, solanin, saponin from guaiacum bark and a saponin from horse-chestnut were employed. For determining the concentration inducing hemolysis, 5% serum-free suspension of rabbit's blood-corpuscles was used. Results were read off after 2 hours. Hemolytic action diminished from cyclamin toward the saponin of the horse-chestnut. The experimental results showed the action of the investigated saponins on trypanosomes and on red blood-corpuscles to run parallel in general. Thus the strongly hemolytic saponins also show strong action on trypanosomes. Nevertheless the limit of concentration determined for the hemolytic action does not indicate the limit for trypanosomes.

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(1c—104)

(1c—104)

**Therapeutic and Toxic Action of Strophanthin on the Frog's Heart.**

*E. Geiger and A. Jarisch, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:52, July 28, 1922.*

The therapeutic action is directed against heart weakness; this encounters resistance at the periphery, either relative, due to decreased

heart strength, or absolute, due to contraction of the vessels. This disproportion must be equalized; the therapeutic action must go back to a corresponding change in the volume per beat and at the same time in the force of systolic pressure, into which a change of frequency may enter as a modifying factor. With digitalis, Frank found that the isometric pressure maximums, corresponding to equal degrees of filling, remained unchanged; with equal or especially with lower filling pressure, there was better diastolic filling; in hearts of warm-blooded animals, increase of isometric maximums, increasing diastolic filling for the same degree of filling pressure, and increase in volume per beat.

As doses of digitalis that were completely effective for sick individuals had no effect in normal ones on amplitude, frequency, blood pressure and diuresis, injury of the heart is apparently a necessary preliminary condition to its therapeutic action. The frog's heart to be examined was injured by decrease of the calcium content in the fluid used to nourish it. It was found that the injured heart, in comparison with the normally nourished one, filled more with the same filling pressure. The diastolic fillings increased and the stretching curve of the isotonic minimums became steeper. The injured heart did not contract so completely with the same filling pressure as the normal and so kept a larger systolic volume. The isometric maximums of the systolic pressure force lay deeper for the injured heart than for the normal one. The curves of the injured heart showed that the heart under lack of calcium became more distensible; with the same filling pressure, the heart took up a greater content in diastole. The systolic change consists in the fact that the heart contents could no longer be driven out so completely.

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(1c—105)

(1c—105)

#### **The Physiologic Action of Simaruba Bark.**

*H. E. Krogmann, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94: 97, July 28, 1922.*

In testing Simaruba bark an extract of 5 gm. root to 50 gm. 70% alcohol was used and the original extract evaporated in a vacuum until of 500 gm. only 3 gm. were left. Half of this was put in hot water, the other half in 96% alcohol. Used on frogs, 0.15 gm. root was lethal for 10 gm. frog. With small doses the heart stopped in systole; with large ones, in diastole. This shows the action on heart muscle. To test its action on smooth muscle the skin-muscle tube of angle worms was used. In order to exclude the action of alcohol, the aqueous solution was used. In both cases there was slowly increasing loss of tonus and cessation of any peristalsis. Excised intestinal musculature was affected in the same way.

In intestines of warm-blooded animals, small doses of Simaruba bark gradually caused a complete stoppage of intestinal movements combined with a considerable decrease of tonus. In Trendelenburg's perfusion preparations, there was contraction of the vessels. The primary action was probably on the end-organs of the sympathetic nerve as is indicated by the general vasoconstrictor effect, though the experiments on rabbits did not show any demonstrable increase in general blood pressure. The field of usefulness of Simaruba bark is, therefore, chiefly

in increased peristalsis caused by inflammatory processes in the intestinal tract, where there is an excess supply of blood and also in catarrh of the intestine, tenesmus and similar symptoms.

(1c—106)

(1c—106)

**Solubility, Capillary Activity and Hemolytic Efficiency of Terpene Derivatives.**

*Heinrich Rhode, Biochem. Ztschr., Berlin, 130:481, July 20, 1922.*

According to Ishizaka's researches, few legitimate relations exist in the case of terpene ketones and terpene alcohols as regards their action on erythrocytes and the surface tension of water. In the menthol and borneol molecule, the abolition of all double bonds resulted in a diminution of hemolytic capacity in comparison with capillary activity, while the accumulation of 3 double bonds, especially in thymol, led to an increase. With menthol and borneol, and less so with camphor, Traube found another physical property, namely the solid state of aggregation at the experimental temperature in contradistinction to the legitimate behavior of the ketones. In accordance with this conception, the hemolytic efficiency of the terpineols, above 35° C., should bear the same proportion to their capillary activity as in most fluid ketones of the menthone and carvone series, while at a lower temperature they should behave similarly to menthol and borneol.

The experiments made use of the purest possible norcamphor, the ketone formed from camphor by cleavage of the methyl group from the ring. Determinations of solubility, capillary activity and hemolysis were carried out. In regard to their influence on the surface tension of an aqueous salt solution in relation to its hemolytic efficiency, norcamphor and  $\beta$  terpineol stood between the solid ketone, camphor; and the solid alcohols, borneol and menthol; although these 3 are fluid at 38°. Norcamphor stood nearer to camphor, the terpineols nearer to the alcohols. Therefore, obvious relations are recognizable which appear at present more closely connected with chemicostructural relationship than with physical properties, at least as far as they are determined by capillary activity, solubility and melting point. The experimental series also showed whether a substance dissolved at its melting point behaves differently in the solution and might, therefore, possess different pharmacologic action than when dissolved below the same. An insight was also gained into the limit of concentration. It was interesting, too, to find that when blood controls were allowed to stand alongside those in which similar blood-corpuscle suspensions had received a slight addition of a terpene derivative, the latter frequently hemolyzed later than untreated specimens. That is not attributable solely to a bactericidal action but conforms to Arrhenius' and Bubanovicz's observation that small doses of hemolyzing narcotics increase the erythrocytes' resistance to hemolysis by hypotonia.

(1c—107)

(1c—107)

**Researches on Internal Disinfection (Experiments with Acridin Dyes in Vitro).**

*P. Wels, Ztschr. f. d. ges. exper. Med., Berlin, 28:347, June 30, 1922.*

Experiments were made with different dilutions of tryptaflavine, with and without guinea-pig organs, to which had been added staphylo-



coccus cultures for testing disinfection. With simultaneous additions of organs and bacteria to trypaflavine solution the organs take up more dye solution and the destructive action of low concentrations of trypaflavine solution is abolished. The same results were obtained with flavicid and rivanol. When organs and bacteria are introduced into the solution the bacteria are destroyed in 64 hours in flavicid solutions (1:30,000) only when the organs are added after the bacteria or simultaneously. Another experiment showed that additions of organs to rivanol concentrations of 1:5000-1:20,000 reduce the bactericidal power of the disinfectant. Finally, the last experiment proved that the action of the organs is also an adsorptive process of the dye as shown by the diminution of the bactericidal power of flavicid solution resulting from transient presence of cotton. From all these experiments the author draws the conclusion that in the application of the disinfectants, not only the blood, but also all tissues compete against the same. The bactericidal property of a definite concentration of a dye may thus be transformed into a stimulative dose.

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(1c—108)

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**The Action of Dakin's Hypochlorite Solution on Certain Organic Substances.**

*N. O. Engfeld, Hoppe Seyler's Ztschr. f. physiol. Chem., Berlin, 121:18, July 29, 1922.*

Dakin assumes that protein substances play a leading rôle among the substances capable of reacting with hypochlorite, but it seems of importance to determine the quantitative chemical action of hypochlorite on proteins, fats and carbohydrates. Halogenated amines were demonstrated by Wurtz in 1850. Halogenated amines are obtained most easily by double decomposition between amines and hypochlorite, namely monochlorin derivatives at ordinary temperature, and dichlorin derivatives by distillation. Hypochlorite deaminizes both ammonia and amines. According to Dakin the antiseptic effects of hypochlorite are explained from the chemical point of view by assuming that certain NH groups of protein substances are converted into NCl groups in the presence of hypochlorite. The substances thus produced (chloramines) produce the same antiseptic action. The assumption that the antiseptic action is due to liberated oxygen is unjustifiable. The action of hypochlorite on carbohydrates, on fat and its hydrolytic products and on protein substances and their hydrolytic products was studied. With the proteins, hydrolysis, deamination, cleavage of carbon dioxid and the biuret reaction were considered. The action of hypochlorite on ammonia and on certain aldehyds was also examined. Glucose gradually loses its reducing capacity under the influence of hypochlorite. Fats are affected very slightly at room temperature, more so at body temperature. Of protein substances, a rapid reaction is obtained with horse serum. At any rate protein substances and their hydrolytic products were influenced much more rapidly than if they had been brought together with fats or carbohydrates. In hypochlorite treatment aldehyds of the next lower stage are formed from the protein substances. In oxidation, particularly in alkaline solution, aldehyds are easily converted into the respective acids. They differ in their

chemical composition and hence also in oxidizability. Formaldehyd and benzaldehyd show a slow reaction, acetaldehyd, salicyl aldehyd and cinnamic aldehyd a rapid reaction with hypochlorite.

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(1c—109)

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**The Action of Aminophenolarsinate of Sodium (189) on Experimental Trypanosomiasis in the Guinea-Pig.**

*A. Navarro Martin and G. J. Stéfanopoulo, Ann. de l'Inst. Pasteur, Paris, 36:619, Aug., 1922.*

The infections examined were *Trypanosoma brucei* and *Trypanosoma gambiense*. The maximum tolerable dose (for guinea-pigs) of sodium aminophenolarsinate is 0.25 to 0.30 gm. per kilo body weight. If an ineffective dose is administered, the trypanosomes may become resistant to arsenicals. The substance (189) effectively cures either of the infections discussed. Its therapeutic coefficient is much more favorable than that of other known arsenicals; 10% aqueous solutions, injected subcutaneously, are well borne and cause no local reaction.

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(1c—110)

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**The Effect of Sodium Germanate upon the Total Hemoglobin of the Albino Rat.**

*Joseph E. Nowrey, Jr., Bull. Johns Hopkins Hosp., 33:341, Sept., 1922.*

Germanium compounds, particularly sodium germanate, have been found to increase the number of erythrocytes in the peripheral blood, but it is not known as yet whether this is a real increase in total blood cells or not. In order to discover whether this drug calls forth an increase in the total hemoglobin, 7 rats were given sodium germanate and 6 were kept as controls. Before the experiment the erythrocyte count and estimated hemoglobin were alike in the 2 groups. One week after the administration of the drug the estimations were again made and then the rats were killed, perfused with normal saline to recover all the blood, and the perfusate diluted to equal in amount the normal rat's blood volume as calculated for its body weight by the formulas of Hatai. Thus the experimenter could compare the hemoglobin estimation done upon a small sample of blood with an estimation done upon a sample of the blood removed and diluted to theoretical blood volume. If Hatai's formulas be valid, this is obviously a method of computing the blood volume of the rat. Results from the control rats confirmed Hatai's formulas. The results of the experimental rats showed that not only were the red cell count and the hemoglobin concentration higher in the treated animals, but also the total blood volume as calculated was higher, as evidenced by a hemoglobin reading in the diluted perfusate which ran constantly higher than in the actual blood of the same animal sampled at the same time. It appears then that sodium germanate increases the hemoglobin as well as the red cell percentage.

(1c—111)

(1c—111)

**Method of Adrenalin Examination in Man.**

*M. Rothmann, Deutsch. med. Wchnschr., Leipsic, 48: 936, July 14, 1922.*

Experiments have been made by numerous investigators, particularly on sick persons, to determine the action of adrenalin under pathologic conditions, in which diagnosis and pathognosis were of primary interest. Generally the adrenalin was injected subcutaneously or intramuscularly and its effect on the blood pressure followed by means of measurements by the method of Riva-Rocci (Recklinghausen), but it was almost never taken into consideration that in the non-narcotized individual the psychic condition may exercise a considerable influence on the height of the blood pressure. None of the physiologists who studied the action of adrenalin on the blood-vessels in animal experiments ever thought of any other method than narcotizing the animal, giving the drug intravenously and determining its action by means of a measuring instrument connected directly with the arterial circulation. In his experiments on man, therefore, the author gave a dose of morphin-scopolamin to narcotize the individual, injected the adrenalin intravenously and measured the blood pressure by means of a Hürthle's plethysmograph, which gives absolute values. There has been great fear of injury from intravenous injection, but Csepai's studies have shown that in small doses of 0.04-0.05 mg. it is not dangerous and that such doses give pronounced rises of blood pressure. Though Csepai did not fulfil the 2 other requirements of the author, still he has made a noteworthy observation: He saw within the first 15 seconds a decrease and then an increase of the pulse which disappeared again after a minute, which is in agreement with the earlier statements of the author that adrenalin causes not only a rise of blood pressure but at first a slowing of the pulse through a depressor-vagus reflex.

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(1c—112)

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**The Influence of Pathologic Conditions on the Destruction of Adrenalin.**

*A. Balint and L. Goldschmidt, Klin. Wchnschr., Berlin, 1: 1510, July 22, 1922.*

The transitory action of adrenalin is caused by its rapid destruction, in which the active factors are alkali content and oxidation. Studies in infants with acidosis showed that the recurrent time of the blood-pressure curve (measure of the action of adrenalin) is lengthened also in premature infants with a low alkali content of the blood. But in infants with fever the recurrent time of the blood-pressure curve was regularly shortened, without an alkalosis having arisen. As the changed alkali content of the blood does not therefore explain the lengthened and the shortened recurrent time, oxidation must be taken into consideration; this is decreased in acidosis and increased in fever. In conditions of overventilation where the carbonic acid tension and the content of the blood in sodium bicarbonate is greatly decreased, the action of adrenalin was markedly decreased. Experiments on Trendelenburg's frog preparations showed that a rapid destruction of adrenalin takes place through oxidation, but only in the presence of

alkalis. Therefore it is probable that in fever and in overventilation the increased oxidation is the cause of the brief action of the adrenalin; the cause of the lengthened action in acidosis is not only the decreased oxidative process but also the decrease in the blood alkalis. The practically important point is that in fever the action of adrenalin is weakened and shortened.

(1c—113)

(1c—113)

**The Action of Placental Extract on Salivary Secretion.**

*Jiro Kosakae, Biochem. Ztschr., Berlin, 130:249, June 20, 1922.*

A dealbuminized and cholin-free placental extract induces uterine contractions and this action is increased by simultaneous exhibition of pituglandol. Animals that received subcutaneous and intravenous injections of the extract showed miosis, salivation and lacrimation. A permanent fistula of the submaxillary and sublingual glands was applied to dogs by Pawlow's method, salivary secretion being observed through the fistula after injection. It was found that the placental extract prepared at 100° C. and placental extract "Ciba" contain a moderate amount of secretin for the salivary glands but that this secretin action appears to be lost at temperatures of 130° C. No increase of the action was detectable with simultaneous administration of pituglandol.

**TOXICOLOGY**

(1c—114)

(1c—114)

**Quantitative Study of the Coöperation of Ions and Organic Poisons. II.**

*Hans Handovsky, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:253, July 4, 1922.*

These investigations aim to make clear the toxic effects of certain salts in increasing the saponin hemolysis of cane-sugar erythrocytes. The first communication dealt with the effect of sodium chlorid. The blood was taken from the ear vein of a rabbit and shaken, the erythrocytes isolated and washed repeatedly in the centrifuge. The latter were suspended in various isotonic mixtures, the volume brought to 100 c.c., and 1% per volume of saponin solutions of different degrees of concentration added; or they were suspended in doubly isotonic solutions of cane sugar or sodium chlorid, brought to 100 c.c., and the desired concentration obtained by mixing both, diluting with water or saponin solution, avoiding local hemolysis. Both methods yielded identical results.

In these tests we are dealing not with chemical reactions between absolutely equivalent units (molecules), but with reactions between units of different ages and therefore different reactive powers: the condition is one of "heterovitality." The suspension of blood-corpuscles is a heterovital system, in which the young corpuscles in sodium chlorid suspension are more resistant to saponin, sodium hydroxid and serum hemolysins. The effect of the following salts was studied: NaCl, NaI, Na<sub>2</sub>SO<sub>4</sub>, Na(SCN)LiCl<sub>2</sub>, MgSO<sub>4</sub>, Mg(SCN)<sub>2</sub>, CaBr<sub>2</sub>, Ca(SCN)<sub>2</sub>. It had been found for sodium chlorid that the increase in the hemolytic action of saponin against cane sugar was proportional to the sodium chlorid and "action concentration" of saponin within certain intervals

of concentration of sodium chlorid. This could be expressed in a formula. More recent investigations show that similar conditions obtain for sodium iodid, while they are much more complicated for sodium sulphate and lithium chlorid. It is still more difficult to decide the matter with regard to salts which are themselves hemolytic (magnesium and calcium). All magnesium salts intensify the action of saponin, the sulphate more than the rhodanate. Cane sugar and magnesium exert an antagonistic effect upon the saponin sensitiveness of the red blood-corpuscles. Traces of cane sugar inhibit magnesium hemolysis, while calcium hemolysis increases with the amount of calcium, irrespective of the sugar content. If a portion of sodium chlorid is replaced by magnesium sulphate of the same molecular weight, the hemolytic action depends on the relation between magnesium sulphate and sodium chlorid. It reaches its maximum if the quotient of  $\text{MgSO}_4 + \text{NaCl}$  is 0.11; it decreases as the quotient rises to 0.25, and then increases again. Calcium salts always increase the hemolytic action of saponin. There is also a maximum for calcium salts. The concentration which is itself most strongly hemolytic, exerts the slightest increasing effect. If calcium chlorid is replaced by calcium bromid, the susceptibility is lessened. Here, as everywhere else, we observe a difference in the behavior of old and young cells. There is no relation between volume and susceptibility of erythrocytes. The increasing effect is probably due to an enlargement of the surface of the blood-corpuscles as a field of attack for the poison which injures the surface. The conception of this increase of the free surface of the blood-corpuscles depends on that of the colloidochemical condition of the cane sugar blood-corpuscles. They are represented as being more gelatinized than sodium chlorid corpuscles. Gelatinization always accompanies a diminution of the degree of dispersion. This renders the corpuscles less sensitive to the poison acting on the surface. Salts have the opposite effect and therefore render cane sugar corpuscles again more sensitive, even if they do not exert any hemolytic action themselves. This is in accordance with the laws governing the augmented adsorption.

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(1c—115)

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**The Use of the Ultramicroscope for Investigating the Action of Poisons on Cells of Bacteria, Erythrocytes and Yeast.**

*L. Traube and P. Klein, Biochem. Ztschr., Berlin, 130:477, July 20, 1922.*

In concentrated and chiefly in aqueous solutions an enormous number of substances are dissolved partly or almost entirely in the colloidal state. In concentrated solutions of substances like amyl alcohol, butyric acid, phenol, anilin, numerous submicrons in the most active brownian movement are present. This principle was utilized for following the action of xylidin, vuzin, octyl alcohol, nonylic acid, m-cresol and thymol on erythrocytes, thrush fungi and yeast cells. Blood-corpuscles were suspended in isosmotic sodium chlorid solution and a saturated aqueous xylidin solution was added. Before long the xylidin microns were adsorbed at the surfaces of the blood-cells, the latter became gradually deformed and the xylidin submicrons penetrated the cells interior. Octyl alcohol had the same action while vuzin caused hemolysis even more rapidly. Adsorption and penetration of the submicrons occurred



very rapidly and the blood-corpuscle outlines became angular. Nonylic acid submicrons penetrated more slowly, but with thymol penetration was very rapid and the blood-corpuscles contracted considerably. No adsorption of submicrons took place with cresol. The blood-corpuscles increased in volume and became spherical; no hemolysis, but flocculation took place. Xylidin was adsorbed by thrush fungi which burst after becoming crowded with submicrons. Hardly any alteration was shown with octyl alcohol and nonylic acid but m-cresol exhibited strong adsorption. Similar pictures of adsorption, penetration, clouding of the plasma and formation of considerable vesicular, as yet not fully identified, structures were observed with yeast cells.

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**Increase in the Rapidity and Intensity of the Poisonous Effect of Some Groups of Poisonous or Pharmacologic Substances on Bacteria and Tadpoles by Variation in Acidity or Alkalinity. A Contribution on Permeability.**

*Richard Labes, Biochem. Ztschr., Berlin, 130: 14, June 20, 1922.*

The precipitating action of a series of alkaloidal salts and of salts of pharmacologically active acids on albuminous colloids, such as denatured serum albumin, depends on H-ion concentration. There is a flocculation optimum which is displaced, with respect to the iso-electric point, toward the acid side by active anions, and toward the alkaline side by active cations. Traube and Overton observed that addition of sodium carbonate to the alkaloidal salt solution increases the rapidity and intensity of the poisonous effect of various alkaloids. Overton seeks to explain the efficacy of the alkaloidal base as against the alkaloidal cations by lipid solubility, Traube, by surface activity. When poisons are allowed to act on tadpoles, bacteria or paramecei in a series of solutions whose alkalinity and acidity are graduated with mixtures of primary and secondary sodium phosphate, or of sodium acetate and acetic acid, increased alkalinity is associated with increased alkaloidal action within all degrees of alkalinity and acidity obtainable with sodium phosphate mixtures. Conversely, in the case of salts (as sodium butyrate and sodium benzoate) in which acid residues determine the poisonous effect, the action is the more rapid and intense the greater the degree of acidity. When lipid solubility is independent of H-ion concentration, as with acetanilid and ethyl urethan, equally rapid and equally intense action occurs at different degrees of acidity and alkalinity. In experiments with staphylococci in which mixtures of sodium acetate and acetic acid were employed for graduating acidity the same conditions as in tadpoles were observed. It is possible, too, that the detoxicating action of alkylsulphuric acids from skatol, indol and similar putrefactive products signifies the formation of the sulphoacids (which are dissociated and lipid-insoluble in the reaction of the organic juices and therefore probably unable to penetrate as easily into the cells) from aromatic substances that are lipid-soluble and rapidly enter the cells from the blood and interfere with the cellular metabolism. In the case of tadpoles the dependence of the action of this group of poisons on H-ion concentration is to be interpreted as a phenomenon of permeability, inasmuch as the substances enter the

blood channel more rapidly in their lipoid-soluble, or surface-active, undissociated form than in the form of lipoid-insoluble ions. Similar rules are not obtainable for substances which cannot occur in any lipoid-soluble or surface-active form, such as potassium and sodium chlorates, arsenates and other poisons.

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(1c—117)

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**Different Stages in the Toxic Action on Isolated Organs.**

*G. L. Schkawera, Ztschr. f. d. ges. exper. Med., Berlin, 28:305, June 30, 1922.*

The vessels of the rabbit's ear were employed for the experiments. Perfusion was performed with different concentrations of Ringer-Locke solution, or cocain hydrochlorid, strychnin nitrate, nicotin (pure), pilocarpin sulphate and atropin sulphate. Three stages have to be distinguished in the action of all poisons: (1) penetration, (2) saturation, and (3) elimination. The different stages frequently show different and often antagonistic action to the same poison. The references in the literature relate mostly to the first stage. Investigations of the second stage show that the physiologic intensity of the action of cocain and nicotin on the vessels runs parallel to the concentration of the poison. If the concentration be reduced rapidly (e. g. with cocain from 1:1000 to 1:5000) the poison is eliminated by the tissues, in which process the reaction of the vessels is similar to that in the freeing of the poison by pure Locke solution. Hence the fixation of the poison by protoplasm is very labile. The eliminating reaction (Stage 3) depends on the concentration of the poison in the preceding saturation stage, on the duration of the preceding perfusion, and on the temperature of the perfusion fluid (the action is more intense with fluid at body temperature). The stronger the concentration of the perfusion fluid in the second stage and the more rapid the return to a weaker concentration (or possibly to pure Locke's solution) the more intense is vascular constriction in the third stage of the cocain experiments. This reaction was entirely preventable by very slow transition to weak concentrations. This eliminating reaction has a definite duration which cannot be influenced immediately by antagonistic poisons (atropin). From this the author concludes that the tissues must first give off the poison as the reaction of the tissue to other poison was abnormal in the saturation and elimination stages. If, in the saturation stage with one poison, a mixture of poisons (containing this poison) be added to the perfusion fluid, the action will differ from that obtained without previous saturation.

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**The Gray Lizard (*Lacerta Muralis*). A Physiologic Reagent for Poisons.**

*Icard, Marseille méd., 59:753, Aug. 15, 1922.*

When the tail of this lizard is severed immediately below the hind legs it is taken with convulsive movements but remains motionless after a few minutes. Its movements, however, can be reawakened for about 45 minutes, by stimulation of the muscular fibers. This

autonomous activity of the tail can also be demonstrated by anesthetizing completely a lizard with chloroform or ether, chloral, etc. The animal does not respond then to any stimulus, but if a red-hot pin is driven into the tail it begins immediately to slash in every direction, the movements continuing uninterruptedly for 3 or 4 minutes; after a short period of rest these can be started again by the same means. Likewise movements of the tail are not inhibited by curare. The relative independence of the tail of *Lacerta muralis* from the nervous centers is therefore such that, without having recourse to any operation, it is possible to obtain certain effects on either the body or the tail with different substances and to determine in this way which act on the nervous and which on the muscular systems. Poisons having a paralyzing effect on the nervous system stop all movements of the trunk and tail, but do not prevent the artificial stimulation of the latter, this being shown by the above mentioned experiments on anesthetized lizards. Poisons of the muscular system, on the other hand, prevent such artificial stimulation. If for instance sulphocyanid of potassium is injected into a lizard, the animal is taken with violent convulsions and dies in a few minutes. The tail does not react then to any stimulation. When a stimulant of the nervous system is used, like strychnin, convulsions are produced in both tail and trunk, but the movements of the former cease immediately after its severance from the body. Finally, if a stimulant of the muscular system (veratrin) is injected, the spontaneous convulsions of the tail will continue after its separation from the trunk. Although certain poisons are spoken of here as stimulants or inhibitors of the nervous or muscular system, it is realized that they have not such sharply defined properties. A substance may, for instance, act at first exclusively on the nervous system and later on the muscles, and different doses of the same drug may have either a stimulating or a paralyzing action.

The same experiments were repeated successfully on different saurians (*Lacerta viridis* and *Platydictylis muralis*) but the tails of other animals, such as mice, were found to possess no power of spontaneous movements.

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**Poisonous Effects. The Action of Quinin and Atoxyl on Liver Lipase.**

*P. Rona and R. Pawlovic, Biochem. Ztschr., Berlin, 130:225, June 20, 1922.*

It was previously reported that the course of poisoning in the system quinin-invertase obeys a different law to that in the system quinin-serum-lipase. In the latter case the poisonous effect, measured by the degree of inhibition of fermentation, is directly proportional to the logarithm of the concentration of the poison. In the former case the poison concentration and inhibition curve corresponds to an adsorption isotherm and all other observations of the action of quinon on invertase likewise support the view that an adsorptive process is involved. These experiments made use of invertase in the form of an aqueous extract of yeast purified with kaolin and of serum lipase in the form of the respective animal species' serum in suitable dilution. It seemed natural to attribute the different behavior of the ferments

toward the same poison to the difference in the medium, possibly in the sense that the ferment's condition is responsible for the mode of poisoning at one time in the aqueous solution and at another in the serum. This assumption seemed capable of experimental investigation. Highly active lipolytic extracts are obtainable from various organs by aqueous extraction. The behavior of these dilute aqueous organic extracts containing lipase toward tributyrin and the poison, as compared with that of the serum lipase under like conditions, might yield information on this question. Experiments in this direction yielded the following results: The fermentative properties of liver lipase, tested by the behavior toward tributyrin, are identical with those of serum lipase. Toward quinin, however, the two ferments behave differently. While 0.01 mg. quinin (in 50 c.c. total volume) inhibits serum lipase, liver lipase is insensitive to 10 mg. quinin under similar conditions. When both ferments are mixed, the resistance or sensitiveness to the poison cannot be transferred from one ferment to the other. Thus, it is possible to detect both ferments and to follow the action of each quantitatively. Liver lipase is much more sensitive to atoxyl than is serum lipase. Even 0.0001 mg. atoxyl (in 55 c.c. total volume) inhibits the ferment. The course of the poisoning obeys the same law as that of serum lipase poisoning. With a concentration of the poison increasing in a geometric series the velocity constants of tributyrin cleavage diminish in an arithmetic series. The poisoning of liver lipase by atoxyl and that of serum lipase by atoxyl and quinin is irreversible.

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(1c—120)

(1c—120)

**The Study of Poisonous Effects. The Combined Action of Quinin and Narcotics on Invertin and the Action of Arsenical Compounds on Maltase and Methyl Glucosidase.**

*P. Rona, Biochem. Ztschr., Berlin, 130:585, July 20, 1922.*

Researches on the action of quinin and invertin tend to show that the poisoning of the ferment, at least in its first stage, possesses the character of an adsorptive process. The form of the poison concentration and inhibition curve and the reversibility of the process and its momentary course and relative independence of temperature, could be explained in this sense. The action of invertin on cane-sugar is arrested reversibly by indifferent narcotics, in accordance with the law of homologous series. In the combined action of quinin and narcotics of the alcohol and urethan series (ethyl and propyl alcohol, iso-amyl urethan) on invertin, the arresting action of the combined poisons on the ferment was always less than the sum of the arresting action of the individual poisons. A displacement of one arresting combination by the other must be assumed.

The action of several arsenical combinations on invertin was also investigated to determine the injurious influence of definite chemical compounds on various ferments. Experiments with arsenical compounds on urease and lipase were carried out. Atoxyl, 0.0001 mg. to 50 c.c. fluid, had a distinct arresting action on liver lipase. Arsenic acid, arsenous acid, atoxyl and methyl arsinoxid were inactive toward invertin. Maltase and methyl glucosidase from beer-yeast were inactive toward arsenic acid, arsenous acid and atoxyl and active toward methyl

arsinoxid. Methyl arsinoxid, 0.3-0.5 mg. in 50 c.c. total volume, inhibited both ferments and with 2 mg. the arrest was complete. The inhibitory action was proportional to the concentration of the poison. Quinin and caffein had no action on maltase or methyl glucosidase. The 2 ferments cannot be differentiated on the basis of their behavior toward these poisons.

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(1c—121)

(1c—121)

**The Oligodynamic Effect of Metallic Poisons on Living Substance. I. Experiments with Paramecium.**

*L. Löhner and B. E. Markovitz, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:417, July 21, 1922.*

The oligodynamic actions of metallic poisons are sufficiently explained by the solution theory. Hence no research is required into their primary physical foundations, but into the quantitative conditions of their poisonous effects. Experiments were made with a view to proving that the law which applies to bacterial cultures, namely that higher concentrations of poison destroy growth, lower ones inhibit it, and still lower ones stimulate it, would also work out in animal life, having been previously demonstrated to be effective for amebas, ciliates, etc. With paramecium also, copper poisoning appears first in the form of a prolonged excitation of a paralytic stage, which eventually leads to death. The exciting stage can easily be overlooked; it is expressed in a moderately increased rate of ciliary motion, in a slightly increased power of locomotion, a diminished tendency to negative geotropism and positive thigmotropism. The paralysis takes a form already familiar from other noxa (suffocation, thermal paralysis, narcosis), i. e. a slowing ciliary motion, a reduced speed and power of locomotion, sedimentation, a slowing of the systolette play, an increase in size of the contractile vacuole, and finally, a cylindric swelling of the entire body due to the accumulation of excretory products.

This stage of advanced paralysis is either followed by gradual death, or the latter is preceded by the formation of cellular hernias, a rupture of the pellicula and a dissolution of the plasma masses. Once the morphologic changes in the nature of a protoplasmic swelling have taken place, the oligodynamic injuries cannot be relieved by placing the paramecia in clean water, while in the early stages they are reversible. The oligodynamic poisonous effect depends on an enrichment of the metal in the living substance induced by adsorption. This is clearly shown, first, by the dying cells of the main mass of paramecia, which become elongated when the same fluid contains a larger number of individuals, and, secondly, by the fact that thoroughly washed paramecia killed by oligodynamy, give a positive fuchsin reaction with Pfeiffer's reagent, in contrast to paramecia killed by other methods.

(1c—122)

(1c—122)

**Cases of Lead Paralysis after Ingestion of New Wine (Must) Containing Lead, with Remarks on Chronic Lead Intoxication among the Peasants of Upper Austria.**

*Georg Stiefler, Ztschr. f. d. ges. Neurol. u. Psychiat., Berlin, 77:25, June 20, 1922.*

The most important causes of lead intoxication are occupational injuries, and after that the use of foods and drinks which contain



lead, which were very frequent in former times. The author observed a case of typical lead intoxication with paralysis of the extensors of the hand and fingers, with partial R. D., colic, blue line on the gums and granulation of the erythrocytes. He found that the source of intoxication was a lead tube which was used in the wine press and which had not been cleaned for a year. The must, of which the patient drank 1-2 L. daily, was found to contain traces of lead. In a group of familial lead intoxications, a wine jug made of defective lead glass was found to be the cause of the condition. Such lead intoxications are not rare among the peasants of upper Austria who use must as a daily drink, as the author can testify from reports of his colleagues and from reports of the public health officers. Flour which contains lead may also cause intoxications; this is caused by the flour being ground on wheels, the axles of which are made of lead. A knowledge of these intoxications is of particular importance for the purpose of making a differential diagnosis from intestinal symptoms. They may be confused with appendicitis.

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(1c—123)

(1c—123)

#### **Lead Poisoning.**

*Wade Wright, Boston M. & S. J., 187: 328, Aug. 31, 1922.*

The author writes of the industrial and clinical aspects of the disease of lead poisoning. The condition is usually of industrial origin, but cases which cannot be traced to industrial exposures are not infrequent, and they may usually be attributed to lead piping of water supplies. House painters constitute a large percentage, but various other painting trades, such as spray painting, dip painting and automobile painting are also responsible for lead poisoning and scores of other occupations, such as those in connection with structural iron work, may lead to plumbism. Exposure to lead is so common that physicians may well keep it in mind as a possible explanation of clinical findings of obscure origin when such findings are analogous to those traceable to poisoning by lead. There is good reason for believing that lead by inhalation is more readily toxic than that received by ingestion.

Trade processes productive of lead laden dusts are more hazardous than those with which dust is not associated. There is a varying degree of the toxic effects upon different individuals. There is a greater degree of susceptibility to lead among women than among men. The manifestations of lead poisoning are many and varied. Although colic, constipation, wrist drop, the blue line, and basophilic stippling of red cells are frequently encountered they do not constitute a clinical picture of the disease. There is no characteristic syndrome. Certain symptoms and signs, however, are more frequently encountered than others such as abdominal pain, vomiting, symptoms of cardiorespiratory disease associated with evidences of nephritis, affection of the nervous system, somewhat indefinite pains in the muscles and pain in the joints. Pallor, loss of subcutaneous fat and progressive wasting are noted as the disease advances.

(1c—124)

(1c—124)

**Pathologic Lesions Produced in the Kidney by Small Doses of Mercuric Chlorid.**

*M. L. Menten, J. Med. Research, 43:315, June-July, 1922.*

Evidence is presented not only of the injurious action on the tissues of mercuric chlorid in exceedingly small doses, but also of the surprisingly short period of time which suffices to bring about these changes. Rabbits were used for the experiments. In the earlier part of the series mercuric chlorid was given combined with food, or passed directly into the stomach through a soft rubber catheter. This method was discarded as unsatisfactory because the retention of the metal for some time in the stomach made it difficult to estimate the effective toxic dose. The intravenous route yielded more exact information regarding the minimal toxic amount and the rapidity of action. Mercuric chlorid, in solution in 0.6% sodium chlorid, was injected into the ear vein. Unless the dose was above 0.005 gm. per kilo of body weight, no immediate effect on the animal could be noted. The quantity of the solvent proved a considerable factor in influencing the toxicity of the drug. If the amount of salt solution injected with the dissolved mercury reached as much as 5 c.c. per kilo of weight, the action of the drug was much more pronounced than if only 0.5 c.c. or 1 c.c. per kilo was used.

Nineteen animals were treated: 5 with 0.0002 gm. per kilo; 3 with 0.0001 gm.; 5 with 0.00002 gm.; 4 with 0.00001 gm., and 2 with 0.000005 gm. per kilo. The animals were killed by a blow on the head. Only those killed 5 minutes after treatment are described since it was found that whenever appreciable lesions occur these are well defined 5 minutes after injection. The liver and kidneys were removed from the body immediately after death. Blocks of the tissue were at once placed in 5% Schering's formalin, imbedded in paraffin, sectioned, and stained with hematoxylin and eosin. The gross changes in the liver and kidneys after a dose of 0.0002 gm. and less per kilo of weight were not marked. The microscope revealed a more interesting picture. In the first and second groups degeneration of the kidney cortex and generally distributed pathologic changes in the liver had occurred. In the third and fourth groups greater variation was noted; the lesions were less marked and in some cases only one organ was affected. In the fifth group the results were negative in the 2 animals studied. The toxic action of mercury appears to be general rather than specific. Because of this nonspecificity, caution should be exercised in the use of even seemingly innocuous doses of mercury in persons with known kidney lesions.

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(1c—125)

(1c—125)

**The Microchemic Distribution of Potassium in Normal Kidneys and in Those in Which Pathologic Changes Have Been Produced by Mercuric Chlorid.**

*M. L. Menten, J. Med. Research, 43:323, June-July, 1922.*

Recognizing the inadequacy of existing methods to furnish a satisfactory conception of the part which the inorganic compounds play in the various tissues, Macallum in 1905 published his microchemical

method for the detection of exceedingly small quantities of potassium in animal and vegetable cells. Among the organs representing a unique distribution of this element is the kidney, chiefly in the cortical tubules. This fact suggested the possibility of using the data obtained by Macallum for the normal kidney as a basis for a comparison with the potassium content of kidneys with definite pathologic alterations, especially such as are limited mainly to the tubules. For the production of pathologic changes mercuric chlorid was chosen. If injected intravenously this salt produces a parenchymatous degeneration of the tubules without a correspondingly severe lesion in the glomerular, interstitial or vascular tissue. The lesions occur within 5 minutes after injection and the degree of degeneration can be regulated by the size of the dose.

Rabbits, guinea-pigs, white rats and frogs were used. In order to obtain organs in which a hypersecretion was taking place, rabbits and frogs were given various diuretics, including caffein, sodium chlorid, sodium sulphate and potassium phosphate. The animals were killed by a blow on the head. The kidneys were removed immediately, cut in sections 5-10 microns thick by the freezing microtome and allowed to fall directly into the reagent; contact with water or other solvent before immersion was thus avoided.

The reagent used for the detection of potassium was the hexanitrite of cobalt and sodium described by Macallum. When fresh tissue is placed in the mixture, potassium forms a bright yellow salt, the hexanitrite of cobalt, potassium and sodium. By repeated washings in ice water the excess of uncombined reagent is removed and the yellow precipitate may then be converted into the black sulphid by the addition of ammonium sulphid. While ammonium salts, if present, may react with the reagent, its salts are very soluble in water and may be easily removed. All sections were mounted in 50% aqueous solution of glycerin.

In the normal kidney the potassium content was found to vary widely. The amount in the cortex far outweighs that in the medullary portion, and even in the cortical part of the organ the potassium in the interstitial tissue and the glomeruli is considerably less than that in the convoluted tubules and loops of Henle. The minimal reaction occurs in the resting condition of the normal cell and the maximal in the same cell in necrobiosis. No sharp line of demarcation can be drawn between the amount observed in excessive diuresis and mild injury. The increase in response to injury is proportional to the injury.

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(1c—126)

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### **The Microscopic Demonstration of Hydrocyanic Acid in Poisoning.**

*H. Brunswik and F. Neureiter, Wien. klin. Wchnschr., 35:623, July 13, 1922.*

The micromethod proposed by Brunswik utilizes the low boiling point (+26°C.) of hydrocyanic acid and is carried out in a glass counting chamber with a 1% solution of silver nitrate and the addition of an aqueous solution of methylene-blue in a hanging drop. A small quantity of the blood (0.5 c.c.) or a portion of the organ to be tested

is moistened with concentrated oxalic acid: the hydrocyanic acid liberated thereby, being lighter than air, rises and produces characteristic crystals of silver cyanid in the drop of silver nitrate, which turns a true blue as a result of the methylene-blue. To make sure that these are silver cyanid crystals, the author advises recrystallization by heating the preparation after adding nitric acid, when the characteristic crystals reappear after cooling. This reaction is so delicate as to be positive even in the presence of 0.06 microgram of hydrocyanic acid.

In animals poisoned by hydrocyanic acid, the poison was demonstrable in the blood, gastric contents and after injection in the area surrounding the site of puncture, though not in the lung after poisoning by inhalation. Animals that were exposed to fresh air for 10 days after poisoning gave positive results, as did also some bread dough that had been mixed with potassium cyanid in 1886. While this method has not been tried in cases of poisoning in man, there is no doubt of its reliability in view of the results obtained in animal experiments. It remains to be determined whether the very minute traces of cyanid combinations reaching the blood in illuminating gas poisoning can be demonstrated with this test, with a view to differential diagnosis between illuminating gas poisoning and coal gas poisoning.

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(1c—127)

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**Adrenal Support in Carbolic Acid Poisoning: Report of Case, with Recovery.**

*C. F. Hayes and Will S. Horn, Texas State J. Med., 18:218, Aug., 1922.*

A 19 year old girl took 1 oz. of carbolic acid on an empty stomach. In spite of prompt administration of an antidote and vigorous treatment in the hospital, 2 hours later she was practically without a perceptible pulse and had cyanosis, bronchial rattling and stertorous breathing. After the administration of 20 minims adrenalin hypodermically she showed such improvement that the adrenalin was repeated every 2 hours. The patient went home the following morning having received a total of 240 minims adrenalin, hypodermically, in a little less than 18 hours. Convalescence was uneventful except for dysphagia and an ulcerative stomatitis, which cleared up after 10 days.

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(1c—128)

(1c—128)

**Poisoning with Oil of Eucalyptus.**

*W. Witthauer, Klin. Wchnschr., Berlin, 1:1460, July 15, 1922.*

A man, 39 years old, after taking about 23 c.c. oil of eucalyptus, had an attack of severe headache, vertigo and vomiting, unconsciousness and frequent convulsions. At the examination 1½ hours later, the patient was unconscious and cyanotic; respiration was stertorous and superficial; the eyes were directed upward, the pupils were dilated and rigid, the pulse was somewhat accelerated; the reflexes were easily elicited and the expired air had a strong odor of eucalyptus. At short intervals there were tonic-clonic spasms of the whole body, turning of the eyeballs, a maximum dilatation of the pupils which were rigid to

light, cyanosis, and arrest of respiration. Gastric lavage yielded a light brown, oily fluid, with an odor of eucalyptus. Another short attack followed, but after blood-letting no further attacks occurred. Although the patient recovered on the following day, he had transitory amnesia. The urine smelled of eucalyptus, contained 0.5% albumin and granular casts. The blood showed a leukocytosis with predominance of polynuclears. After a few days the patient was discharged entirely recovered.

Oil of eucalyptus owes its poisonous effect to phellandren and poisonous camphors and terpenes, which affect the living protoplasm. The cell undergoes high oxidation, resulting in burning of the cell or an accumulation of injurious oxidation products, while on the other hand, the cells themselves give up oxygen to the oil of eucalyptus. The increased accumulation of carbonic acid and the insufficient intake of oxygen results in respiratory paralysis, cyanosis and convulsions.

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(1c—129)

(1c—129)

**Death Following the Administration of Thymol.**

*Milford E. Barnes, J. A. M. A., 79:964, Sept., 16, 1922.*

Attention is called to the large number of cases of safe administration of this drug, lest the real value of it be overlooked when its toxicity is emphasized. On the other hand, the large number of safe administrations is liable to cause laymen and even medical officers to grow somewhat lax and to forget or ignore the fact that they are dealing with a drug which, when absorbed, is highly toxic. In Siam, the following rules have been adopted for the administration of thymol: a preliminary small dose of magnesium sulphate is taken the evening before treatment; no breakfast permitted on day of treatment; at 7 a.m. 20 gr. of thymol mixed with an equal amount of lactose is administered in capsule; at 9 a.m. an additional dose of 20 gr. of thymol; at 10 a.m. a final purgative dose of magnesium sulphate in hot water.

The first patient had not taken the preliminary dose of salts. She had applied for treatment for tapeworm infestation. The medical officer considered her to be well able to take the treatment; he administered in a single dose 40 gr. of thymol. In 20 minutes she felt slightly dizzy and a purgative dose of magnesium sulphate was given. Patient started home, fainted and died 3 hours after taking the thymol. Possibly a cardiac or thyroid involvement existed which escaped the notice of the medical officer. Thymol poisoning was the direct cause of her death. The second patient also applied for treatment for tapeworm infestation. She suffered from pulmonary tuberculosis but was given 20 gr. of thymol at first dose and 10 gr. at second dose. By the seventh day pneumonia had developed and on the ninth day she died. Although the immediate cause of her death was pneumonia developing in tuberculous lungs, the absorption of thymol was a contributory cause.

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(1c—130)

(1c—130)

**A Case of Horse-Radish Intoxication.**

*Heffter, Klin. Wchnschr., Berlin, 1:1561, July 29, 1922.*

A woman who had previously been well worked for 3 hours in putting up 5 kg. of freshly grated horse-radish and during the work used



spectacles and other protective measures. Shortly before she finished the work she had lacrimation, cough and severe headache. In the next 3 days the conjunctivitis and headache increased to such an extent that she could not sleep for several days and nights, and she had severe pain in the limbs, vomiting, defective hearing and bronchial catarrh. The irritative symptoms of the mucous membranes persisted for weeks. Electric-light baths brought about temporary improvement. The clinical picture resembled that after inhalation of certain war gases and nitrous gases, as the severe symptoms did not develop until after some hours. Other persons who helped in the work were affected similarly but to a lesser degree.

## 1d. BACTERIOLOGY AND PARASITOLOGY

(1d—147)

(1d—147)

### Indicators for Culture Media Containing Varying Acids and Buffers.

*I. Walker Hall, Brit. J. Exper. Path., London, 3: 182, Aug., 1922.*

The author's investigations on this subject include a study of (1) comparative buffer indexes of mediums pH 7.6 and equal amino-acids containing dilute acids, (2) effects of storage on buffer indexes in the presence of various acids, (3) effect of blood on buffer indexes, (4) comparison of colorimetric and E.M.F. readings. The author's tabulated results show that brom-phenol blue, methyl red and phenol red may be used as pH indicators for bacteriologic mediums containing dilute quantities of certain typical mineral and organic acids. Buffer indexes of mediums are slightly altered when small amounts of blood or of dilute acids are added. They are unaffected by storage.

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(1d—148)

(1d—148)

### A New Peptone Preparation for Bacteriologic Practice.

*Vieth and Kathe, Deutsch. med. Wschnschr., Leipsic, 48: 1076, Aug. 11, 1922.*

Because of the great difficulty in procuring Witte's peptone the author tried to find a dry peptone that would be equal to it in every way and could be used for all bacteriologic purposes. He made experiments with fibrin and mixtures of fibrin and serum albumin, hemoglobin, fresh blood and whey albumin, but peptone of high quality could only be obtained with the use of meat. In order to obtain as pure a peptone as possible and free of inorganic salts, it is advisable not to use hydrochloric acid for peptonization but sulphuric acid and finally to precipitate the sulphuric acid with baryta. The peptonization should not be carried too far, as otherwise the more exacting bacteria do not thrive well. The chief difficulty lay in producing a peptone that permitted indol formation and at the same time gas development from grape sugar by suitable bacteria. Comparative studies were made with the prepared peptones and Witte-peptone nutritive media with typhoid-paratyphoid bacilli, Gärtner's bacillus, dysentery bacilli and the colon group, with proteus bacilli and cholera vibrios, with diphtheria strains, Staphylococcus aureus, streptococci and staphylococci and with bacteria of the

typhoid-paratyphoid-dysentery group and also comparative tests for antigenic properties. Moreover, antiformin extracts of cholera vibrios grown on both sorts of agar were prepared and used as antigens in complement fixation experiments, and finally toxins were made from a strain of diphtheria in both bouillons and tested on guinea-pigs by the intracutaneous method. In all cases it was found that peptone 93, that can be obtained under the name of peptone Knoll, is of equal value with Witte's peptone, and it was found by other investigators that this also held good of the pharmacologic action of the preparation. Peptone Knoll is recommended as a peptone preparation of high quality.

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(1d—149)

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**Growth of Bacteria on Vegetable (Leguminous) Mediums.  
Attenuation of Diphtheria Toxin in Bean Broth.**

*N. Pane, Riforma med., Naples, 38:745, Aug. 7, 1922.*

The author has attempted to discover, in the first place, to what extent the meat juice in culture mediums (Koch's method) could be replaced by decoctions of leguminous seeds—peas, lentils, beans. To this end, 100 gm. of such dry seeds, of the best quality, are placed in 1 liter of fresh water; after 24 hours there are added 5.5 gm. sodium chlorid, and the mixture is placed in the autoclave at a temperature of 118° C. for 1 hour. After cooling of the decoction by passage through glass flasks, and after sedimentation of the seed fragments, the supernatant fluid is decanted off and filtered. This filtrate may be used for the preparation of broths, agar or gelatin mediums in the usual manner, with the addition of 1% peptone. All manner of bacteria grow luxuriantly in such mediums.

These leguminous decoctions possess the striking advantage of permitting unstinted development of numerous species of microorganisms, more particularly those concerned with intestinal infections, without absolutely requiring the addition of peptone. This is explainable by the fact that these decoctions contain, in addition to various salts, also substantial quantities of legumin in solution as well as carbohydrates—this is particularly true of peas—whereas filtered meat broth contains only traces of gelatin and glucose. Sedimentation and filtration of leguminous decoctions prepared in the manner described render possible the obtaining of a perfectly clear solution of legumin, which becomes cloudy only on addition of acetic acid (the greatest amount of cloudiness is obtained with bean decoctions). An interesting observation in connection with these decoctions (of peas or beans) is that the bacteria grown therein retain their vitality for months; in some cases such vitality was observed one year following inoculation. This fact enhances the value of leguminous culture mediums for laboratories and other institutions where it is impossible to effect frequent transplantations of bacterial strains—with a view to conserving their vitality and virulence—through the various usual culture mediums containing peptone and meat broth, in which the life term of some bacterial strains is rather brief.

The author has been able to demonstrate repeatedly, by means of animal experiments, that highly virulent and toxic bacteria, particularly the diphtheria bacillus, when grown and kept in emulsions made from

leguminous seeds, lose a considerably greater portion of their pathogenic proclivities as compared to similar bacteria cultured in peptonized meat broth media.

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(1d—150)

(1d—150)

**Photographic Methods for Making Permanent Preparations of Bacterial Specimens which Easily Become Decolorized.**

*Guido Reina, Policlinico (Pract. Sect.), Rome, 29:1043, Aug. 7, 1922.*

With a view to obtaining microscopic specimen preparations which should retain their practical utility for several years, particularly for teaching purposes, the author has attempted to introduce photographic technical methods in staining microorganisms nonresistant to Gram's stain, and reports highly satisfactory results. This new technic is now available as part of the armamentarium of any laboratory, since it possesses the additional advantage of ease of application.

This photographic technic is uniformly followed by good results if properly and carefully carried out, as Golgi, Cajal and others have done in their studies of the nervous system or of spirochetes in tissues. However, the author has introduced some modifications, affecting more particularly the various components of the fixing fluid and the length of exposure to the different reagents. His fixing fluid is a mixture of formalin, uranium nitrate and alcohol; from this mixture the preparations are passed through solutions of silver nitrate and hydrochinon plus sodium sulphite. After drying and sectioning, the sections are treated with gold chlorid, sodium hyposulphite and ammonium sulphocyanid. For staining the background the best results are obtained with carmalum, the bright red color of which forms a vivid contrast with the jet black coloration of the included bacteria.

The preparations thus made are superior to those stained by the usual methods since (a) they are certain to last a much longer period of time, and (b) the black stained bacteria stand out in marked contrast against the bright red color of the tissues within which they are located.

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(1d—151)

(1d—151)

**The Phenomenon of Capillary Ascent in the Differentiation of Bacteria.**

*C. Cipriani and L. Fanzio, Policlinico (Med. Sect.), Rome, 29:426, Aug. 1, 1922.*

The method of differentiation of bacteria by means of capillary ascent in the filter paper was instituted by Friedberger, following similar investigations by other authors. Immersing, for about 20 seconds, the lower end of strips of filter paper, 10 cm. long and 1 cm. wide, held vertically, in bacterial suspensions prepared with 10 c.c. of physiologic solution and colon bacilli and typhoid bacilli, in various proportions, and suspending them then for 10 minutes in closed sterile tubes (until the liquid rises in the strips to 8 cm.) it is found that the typhoid bacillus rises to the higher part of the strips, while the *B. coli* remains in the lower part; this result is evident if, after imprinting the strips (without pressure) on Endo plates these are left in the thermostat for

24 hours; colorless colonies of the typhoid will develop in the part corresponding to the upper end, clearly divided from the red colonies of coli which develop in the part imprinted with the lower end of the strip.

The authors repeated the experiment and found that the best filter paper to use was that of Schleicher and Schull No. 597 (not being able to find that used by Friedberger). They immersed the strips for 4-5 mm. for 3 minutes, leaving them then suspended outside the liquid for 5 minutes; imprinting the strips on Drigalsky media, they were able to show, after 24 hours, that the coli had arisen to 3-4 cm. and the typhoid bacilli to 6-7 cm.

To apply the method to bacteriologic examination of feces, the authors used special means: dissolving the typhoid feces in physiologic solution and leaving that to settle, then mixing 5-6 c.c. of the liquid above the sediment with as much ox-bile, leaving the mixture in the thermostat for 24-48 hours, then mixing 8-10 drops of such culture with 50 c.c. of physiologic solution and on this liquid practicing the method of capillary ascent. The method gave positive results in all cases of typhoid feces emitted in the second or third week of the disease; an important result, if compared with 23.4% and 33% of positive bacteriologic results obtained with the ordinary methods in the second and third weeks of the disease. The number of cases of typhoid examined by the authors is, however, small. The phenomenon of the different heights of capillary ascent of the germs is not yet very clearly understood; it has been demonstrated that it does not depend upon either the difference in mobility of the germs, or upon their specific gravity; Klinger has recently offered the hypothesis that the phenomenon depends upon different properties of the individual germs to surround themselves with substances soluble in water; the colloidal particles would form themselves on the surface of the fiber of the paper the more easily the less they are protected by a capsule of water.

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(1d—152)

(1d—152)

**Experimentally Demonstrable Relations between the Virus of Epidemic Encephalitis and That of Febrile Herpes.**

*Schnabel, Klin. Wchnschr., Berlin, 1:1685, Aug. 19, 1922.*

In connection with 4 cases of epidemic encephalitis, the author made animal experiments with the spinal fluid, saliva and smears from the pharynx. Three of the cases were in the chronic stage. The subdural inoculation of lumbar punctate from these 3 was negative in rabbits. The saliva of one patient was infectious for the rabbit's cornea. The fourth case was an acute one. The sediment of the punctate of the latter patient was floated in a small amount of spinal fluid, and 2 rabbits inoculated corneally and 4 subdurally. Of all the animals only 1 showed typical symptoms after 7 days, and this 1 was killed and examined. A part of the cerebrum was put in glycerin for perservation, another was used for further animal passage, and the rest, together with the cerebellum and medulla, was used for histologic examination. In the latter, in addition to the degenerative-necrotic changes around the trephine opening due to trauma, there was a pronounced infiltration of the meninges with slight perivascular accumulations of

cells in the region of the midbrain and medulla, consisting chiefly of mononuclear leukocytes. Degenerative changes in the ganglion cells of different parts of the cerebrum completed the histologic picture.

In view of the source from which the lumbar punctate was obtained and the findings in animal experiment, the assumption seems justified that the virus obtained was encephalitis virus. With a small amount of the brain emulsion from the first rabbit further animals were infected. One animal died on the seventh day with typical symptoms of encephalitic general infection, the others on the succeeding days with the same symptoms.

A passage virus cultivated from the lumbar punctate of a case of acute encephalitis caused clinical symptoms in rabbits and also in guinea-pigs and white mice, which were characteristic of encephalitis virus. Further experiments served to show the relationship of this virus to that of febrile herpes. The material used for comparison was a brain passage virus obtained from a rabbit which had died from a general disease after corneal inoculation with the contents of herpetic vesicles in a man; the virus was preserved in glycerin.

(1) The rabbits, which  $2\frac{1}{2}$  months before had had a right-sided keratoconjunctivitis after infection with the vesicle contents of a fresh herpes labialis, were infected, at the same time with 2 untreated control animals, with a fresh brain emulsion of the above-mentioned encephalitis strain ("Berlin"), by instillation into the conjunctival sac of both eyes. One remained well, 1 showed after 6 days' incubation a slight conjunctivitis of the left eye which healed without sequels after 3 days. The control animals both had a severe keratoconjunctivitis of both eyes and died as the result of the general infection which followed it.

(2) The rabbits which 2 months before had also had a herpetic keratoconjunctivitis were infected intradurally with virulent encephalitis strain "Berlin." While the control animals infected at the same time intradurally died after 5 and 8 days with the characteristic general symptoms, the rabbits M 70 and M 71 remained quite well. The results were the same in experiments in which 2 animals that had survived a keratoconjunctival infection with the encephalitis strain "Berlin" for 1 or 2 months were then infected conjunctivally or subdurally with herpes passage virus; in neither case did they take the disease. Only 1 rabbit, which in the preliminary treatment had had symptoms only in the right eye, had a slight conjunctivitis of the left eye for 4 days without involvement of the cornea.

The clinical symptoms and pathologico-anatomic changes caused by the herpes virus were just the same as those caused by the encephalitis virus. A close relationship but not an identity is indicated by the fact deduced from the protocols of the experiments that the rabbits that had survived a unilateral keratoconjunctivitis had a reaction, on reinfection, though a slighter one in the eye that had not been affected before. But such findings cannot be given decisive significance, because under some circumstances under otherwise equal conditions they may be observed in reinfection with homologous virus (the same virus used for the preliminary treatment). Experiments would be decisive if they demonstrated identical cell inclusions in experimental herpetic and encephalitic infection in the corneal epithelium and in the ganglion cells. Such experiments are under way and will be reported later. The question is important as to whether the encephalitic passage virus is identical with



the causative agent of encephalitis in man. From the findings thus far there is no reason to doubt that it is.

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**The Transmissibility of Herpes Genitalis to the Rabbit.**

*Luger and Lauda, Klin. Wchnschr., Berlin, 1:1608, Aug. 5, 1922.*

After transferring the vesicle contents in a case of herpes genitalis to the cornea of 2 rabbits, in 1 case, after an incubation of 24-48 hours, there was a herpetic inoculation keratitis with the characteristic branching, the epithelial defects, the formation of vesicles and umbilication and the filtrates, and on the third day conjunctivitis and diffuse turbidity of the cornea. After 10 days, the signs of irritation disappeared and pannus developed which ended in complete healing or scar formation. The keratitis could also be transmitted by passage from rabbit to rabbit. Histologic examination of the inoculated cornea showed on the second day partial epithelial defect, balloon-like degeneration of the epithelial cells, leukocytic infiltrations in the epithelium and in the upper layers of the cornea; and in the nuclei of the epithelial cells and the corneal bodies, the same degenerative changes as in herpes febrilis. In the corneal infection, there were no herpetic general symptoms but they appeared after intravenous injections and also after intravenous and subdural inoculation of brain emulsion from animals that had died with general symptoms. These experiments show the identity of the virus of herpes genitalis and herpes febrilis, the more so because, in crossed animal experiments, there was immunity of the cornea to herpes genitalis after inoculation with herpes febrilis and vice versa.

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(1d—154)

(1d—154)

**The Motility of Anaërobic Bacteria, and a New Method of Greatly Increasing Motility.**

*M. van Riemsdijk, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:679, Aug. 12, 1922.*

The higher the organization of an individual the greater is the differentiation of movement of which he is capable. Thus man, with his highly organized nervous system, has the finest and most subtle degree of motility. The lower groups display more specific movements, characteristic of the species, and less individual differentiation. Thus the typical ameboid motion differs from the system of motility of the flagellates and of the ciliata. Among the unicellular organisms—the bacteria—also, differences in specific movements occur. The active motion of these various groups depends upon: (1) age of the cells; (2) temperature; (3) light; and (4) nature of the available nutrition, and other factors.

The anaërobes display a remarkable degree of individual variation in motility, one microscopic field frequently revealing all types of motion from violent activity to complete immobility. Van Riemsdijk suspected that oxygen played a part in this variability, and evolved a mode of examination by the hanging-drop method under oxygen-free conditions. A glass ring, dipped in sodium salicylate, was placed in the center of

a preparation slide, and a smaller glass ring placed within the first. The entire slide was dried at 37° C., or by exposure to room temperature for 24 hours. The space between the 2 glass rings was divided, by means of melted paraffin, into a large and a small chamber; B and A respectively. Into A, 3 drops of pyrogalllic acid were placed; 9 drops of 10% potassium hydroxid were placed in B. The upper edge of the large glass ring was moistened with sodium salicylate, and a cover-glass 24 by 24 mm. in size was prepared with a hanging drop and laid over the preparation slide so that the drop was directly above the small chamber. As soon as the cover-glass was completely dry, the pyrogalllic acid and the potassium hydroxid were carefully shaken together, until the mixture was dark brown. A temperature of 37° C. was then applied for 5 or 10 minutes. The preparation was then examined microscopically, the objective being concentrated on the light central space. By means of a hydrophilic gas indicator, it was demonstrated that the oxygen disappeared from the chamber within 10 minutes. In this manner a number of anaërobes were examined, and their motility determined. In the case of most of the strains the motility was greatly increased by the anaërobic conditions. The individual variation in degree of motility disappeared; the cells presented the form of motility characteristic of the species. *Bacillus* of Novy (causative organism of malignant edema) appeared to be affected by the presence or absence of oxygen. *Bacillus butyricus* Beyerinck, and *B. butyricus* Grassberger and Schattenfroh, presented more activity when oxygen was present than otherwise; this may be an example of the fact that small doses of a poison exert a stimulating effect. Salvarsan, in low concentration, has been observed to stimulate *Spirochaeta pallida* to increased motility; thallium salts increase the acid production of *Bacillus acidi lactici*. Narcotics stimulate flagellates, if administered in greatly diluted form. The anaërobes present individual variations in oxygen tolerance. This is important from the diagnostic point of view.

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**A Method for the Separation of Spore-Bearing Anaërobes from Other Spore-Bearing Bacteria.**

*J. Howard Brown, J. Lab. & Clin. Med., 7:692, Aug., 1922.*

The author experienced considerable difficulty in the separation of anaërobes from facultatively anaërobic spore-bearing bacteria until the method to be described was employed. Satisfactory results were obtained by incubation of the material under investigation in fluid media under strictly anaërobic conditions for several days, then heating the mixed culture for 20 minutes at 80° C. It was found that under strictly anaërobic conditions the facultative anaërobes did not produce spores, or at least none were found within the period of incubation of 1 week. Incubation must be long enough to permit the anaërobes to produce their spores. If certain of the facultative anaërobe spores do survive the anaërobic cultivation and the subsequent heating they are not present in sufficient numbers to cause serious difficulty in the isolation of the anaërobes. After the vegetative forms have been killed by heat the mixture may be plated anaërobically at once or after germination of the spores in fluid media. For obtaining the growth of a large number

of anaërobes of various kinds it has been found advisable to inoculate original material into at least the following 3 media under vaselin in test tubes, (1) cooked meat medium, (2) dextrose bouillon, and (3) sugar-free bouillon. Sterile tissue may be added to the last 2 if desired.

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**A Pleomorphous Bacillus Producing Special Spherical Bodies (Spore Form?) Isolated from the Pus of a Pyonephritic Sac.**

*Guido Vernoni, Policlinico (Med. Sect.), Rome, 29:411, Aug. 1, 1922.*

From the pus of a pyonephritic sac, in a subject probably tuberculous, there has been repeatedly isolated and cultivated a bacillus, agglutinatable even in strong dilutions of the blood serum of the patient. This germ has been shown to be pathogenic for guinea-pigs by peritoneal injection. In culture it has shown marked polymorphism, by the variable dimensions and forms of the bacillary elements, by the formation of very long filaments, sometimes braided to form a sort of web or membrane (but ramifying) and by the great variation of the colonies on gelatin. In the first cultures on solid media, especially on potato, maintained at 20-25° C., there is developed from the bacillary body, special spherical formations, similar to common spores, without possessing, however, either the bacteriologic character (heat resistance), or the biochemical character (resistance to decoloration) of these. Efforts have been made to produce the formation of these spherical bodies by means of artificial cultures, but without success in obtaining forms as typical as those spontaneously produced.

Various hypotheses have been formulated as to the nature of these spherical bodies (degenerative forms, spore forms?) with a leaning toward the theory that they are proper elements of the vital cycle of the germ that accompany it in special biologic contingencies, like certain changes in the general conditions of life (parasitic life, saprophytic life, in natural surroundings or in the cultural surroundings of the laboratory).

As to pathogenic action, the germ may be considered as an agent in renal suppuration.

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**The Cultivation of Bacterium Abortus Bang.**

*C. P. Fitch, J. Infect. Dis., 31:233, Sept., 1922.*

A cylinder of commercial CO<sub>2</sub> was used in place of the generator used by Huddleson. The medium which gave the best results was beef infusion agar, made from lean beef, and 2% agar added. It should be adjusted to a pH of 6.8 to 7.2. A slightly more alkaline medium than hitherto reported was found to be better for the growth of Bacterium abortus Bang. At the time the medium is to be used, about 10% naturally sterile horse serum should be added to the melted agar, cooled to 50° C. and the tubes allowed to solidify in a slanting position. The tubes are then heavily seeded and placed in a round Withal Tatum museum jar with a known capacity. The cover is raised sufficiently to

allow the rubber tube from the carbon dioxide tank to enter and approximately 10% of the gas to be added. The tube is removed quickly, the cover screwed tight, and the jar placed at 37.5° C. After 24 hours' incubation small pin-point colonies will be noticed on the medium, and 48 hours' incubation shows well developed colonies of *B. abortus*. This method has given the best and most uniform results.

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**Hydrogen-Ion Concentration and Bacillus Coli. I. Acidogenic Capacity of B. Coli. II. Bactericidal Effect of Definite Hydrogen-Ion Concentrations on B. Coli.**

*Kurt Scheer, Biochem. Ztschr., Berlin, 130: 535, 545, July 20, 1922.*

I. It appears important to investigate the relations of H-ion concentration to individual species of bacteria particularly in order to determine general laws and the behavior toward *Bacillus coli*. On the one hand, this bacillus is itself strongly acidogenic, while on the other hand, it can exist under the most diverse external conditions as well as within the body in the different intestinal sections. It must be able therefore to adapt itself to changing conditions and to enter into relationship with the acid reaction of its environment in a varied manner. No indicator method could be employed as the determination of the ions demands great accuracy. The values were therefore determined throughout by measurements in the gas-cell. The H<sup>+</sup> produced by acidification of sacchariferous buffered nutrient bouillon by *B. coli* rises in the first few hours to pH 5, increases very slightly thereafter and attains a final acidification value in 1-2 days. This behavior respecting velocity and final value is approximately the same for all investigated strains and cannot be brought into relationship with other characteristic properties, such as Nissle's antagonistic index and the stability against malachite green of some strains. The attained final acidification value is approximately independent of the investigated human strains and of the initial H<sup>+</sup> of the nutrient bouillon. On the other hand the final value is influenced by the sugar variety and possesses a definite magnitude for each kind of sugar. Thus, it is about pH 4.7 for milk-sugar and pH 4.5 for glucose. It is, however, constant for a definite sugar variety and represents a characteristic magnitude for the *B. coli*. The final value is also influenced (diminished) by addition of lactic acid or acetic acid provided the altered initial H<sup>+</sup> does not immediately attain or exceed the final value.

II. It is of importance to determine at what H<sup>+</sup> *B. coli* is able to exist and with what pH it is destroyed. Former experiments made use of acetate mixtures the pH of which was measured by a gas-cell for determining what H<sup>+</sup> acts bactericidally. The mixtures inoculated with *coli* were kept in the incubator and from them streak cultures were made on Endo agar at definite intervals. These results were controlled in bouillon acidified with increasing amounts of 0.1 n. HCl and inoculated with *B. coli* 100. It was found that colon bacilli are capable of acidifying in a nutrient medium containing glucose up to pH 4.5 and higher, thus exceeding the limit at which they were formerly supposed to be destroyed. Generally, *B. coli* was destroyed within definite periods by definite H-ion concentrations, namely within 24 hours toward the acid side at pH 4.6 and toward the alkaline side at pH 9.4. The bactericidal

pH 4.6 is attained or even exceeded during formation of acid in sacchariferous nutrient fluids by *B. coli* itself, so that the bacilli destroy themselves in a certain time. Accordingly, the hitherto supposed regulatory mechanism, which was assumed to protect *B. coli* against formation of acid up to injurious  $H^+$ , is nonexistent.

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**The Promotive Action of Charcoal Suspensions and Other Substances with Great Surface Area, such as Colloidal Silicic Acid, Ferric Phosphate and Agar-Agar, on the Formation of Fermentative Gases by Bacillus Coli in Albumin-Free Nutrient Solutions.**

*Richard Labes, Biochem. Ztschr., Berlin, 130: 1, June 20, 1922.*

In an attempt to obtain an albumin-free nutrient solution which would favor the fermentative activity of the coli bacillus, the following was composed: glucose (varying from 3 to 0.3%); magnesium sulphate 0.01%; sodium chlorid 0.18% (replaceable largely by potassium chlorid); potassium chlorid 0.075%; ammonium lactate (varying from 0.63 to 0.063%; in place of ammonium lactate other nitrogen sources—ammonium chlorid, asparagin, ammonium succinate or even urea—could be employed with the same result but without a nitrogen source no fermentation took place); calcium chlorid 0.01%; further, for varying and regulating H-ion concentration, concentrations of primary and secondary sodium phosphate varying from 0:3.0 to 2.5:0.5, wherewith the total phosphate content could rise up to 1/16 molar.

The aforementioned varying experimental series were observed in a small fermentation saccharimeter as regards the fermentation gas column. The experiments showed that suspensions of different finely divided substances such as charcoal, silicic acid and ferric phosphate are able to exercise a highly favorable influence on the formation of fermentation gas. The common characteristic of all these substances is the great superficial development which may lead to differences in the concentration of biologically active substances (gases, metabolic products, nutrient substances), between the limiting surface and the solution, by adsorptive effects. The favorable influence is found in slightly alkaline, as well as in slightly acid, original solutions and the suspensions act by abolishing the supersaturation of the nutrient solution by fermentation gases, which is unfavorable to the bacilli, by uniting these gases to form gas bubbles at their surface.

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**The Sonne Dysentery Bacillus in Australia.**

*S. W. Patterson and F. E. Williams, J. Path. & Bacteriol., Edinburgh, 25: 393, July, 1922.*

The authors describe the characteristics of a group of bacilli, corresponding to the dysentery bacillus of Sonne, isolated from cases of dysentery in Australia. A patient died with gastro-enteric symptoms, and showed postmortem typical dysenteric ulceration of the large intestine; MacConkey plates showed numerous colorless colonies. The Gram



negative bacilli from these were nonmotile, gave acid fermentation without gas formation in glucose and mannite-peptone water, and left the lactose media unchanged. Emulsions in 0.85% saline solution were agglutinated with Flexner serum in a dilution 1/400, but not with Y serum. In the preliminary classification they were regarded as low agglutinating Flexner dysentery bacilli. Further investigation showed that the colonies were larger than true dysentery colonies, and after 24 hours' culture on plates were more opaque, with thickened center and more spreading margin; but they remained colorless for over a week. They turned lactose peptone water acid, however, on the seventh to the tenth day, usually the ninth day; and, after subculture in lactose media, the acid fermentation occurred earlier. Intraperitoneal injections of 24 hour agar cultures of strains in rabbits caused intestinal ulceration and death.

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**The Mathers Coccus in the Throat in Influenza.**

*F. W. Mulsow, J. Infect. Dis., 31:291, Sept., 1922.*

During February and March, 1922, an epidemic of a highly contagious disease (so-called influenza) of short duration and followed by few complications occurred in Iowa City. The bacterial content of the throats of the students of the second year medical school before, during, and for some time after the epidemic were studied. Cultures were also made from the tonsils and nasopharynx of patients sent to the hospital with influenza, and of other students with similar symptoms. Hemolytic streptococci were present in 47% of the students examined 2 or more times, and appeared in smaller numbers during an attack of influenza. The pneumococcus was isolated from 15 students and Type IV was found in 12 of these. The influenza bacillus could be isolated more often from the normal throat than from the throat of influenza patients. A green-producing streptococcus resembling the pneumococcus in morphology but insoluble in bile was the predominating organism in an influenza epidemic affecting 75% of a class of students. The same organism was found to be predominant in the throats of other students with similar symptoms and in the throats of patients in the hospital with influenza. This coccus grows characteristically on blood agar and uniformly ferments dextrose, levulose, maltose, sucrose and lactose. In most cases inulin, salicin and raffinose are also fermented. Dextrin and mannite are not fermented. The coccus is only slightly virulent for mice and rabbits. The relation of this organism to the epidemic is very interesting. The name *Streptococcus mathersi* is suggested for this organism because of Mathers' early study of it in relation to influenza.

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**The Nature of the Action of Potato upon the Growth of *B. Influenzae*.**

*Paul Fildes, Brit. J. Exper. Path., London, 3:210, Aug., 1922.*

In the author's experiments potato juice was prepared by passing peeled potatoes through a mincing machine and then through a press.

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The resulting brownish fluid heavily charged with starch grains and débris was diluted with an equal quantity of saline solution and filtered through paper pulp, a coarse "English" Berkefeld candle, and finally a Berkefeld N to sterilize. The action of this potato juice, heated and unheated, upon the growth of *Bacillus influenzae* was then tested, the amount of growth being judged by opacity, checked by microscopic examination and subculture. The resulting stimulating action of potato upon the growth of *B. influenzae* is due, the author suggests, to the action of the peroxidase enzyme operating in the same manner as blood pigment to accelerate the transfer of atmospheric oxygen to the bacillus.

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**The Source of the Microorganisms in the Lungs of Normal Animals.**

*F. S. Jones, J. Exper. Med., 36: 317, Sept. 1, 1922.*

It was known that the larger herbivora harbored organisms, but some doubt existed as to the presence of bacteria in the lungs of laboratory animals. Their possible source and significance seemed of particular importance. With these points in view a bacteriologic study of the lungs of normal calves, rabbits, guinea-pigs, mice, and rats was undertaken. Relatively simple mediums, such as slanted agar and agar to which a few drops of defibrinated horse blood had been added, and veal infusion bouillon were employed. The bits of lung tissue were pushed down over the surface of the slants into the condensation fluid, and all tubes sealed with sealing wax, and incubated for 14 days at 38° C.

Among the herbivorous animals the proportion of tubes showing growth was consistently high, 75% in the case of the guinea-pig to 85% in the instance of the calf. The proportion of positive tubes from the mouse and rat was much lower, 31% and 38% respectively. The tissue cultures, when examined frequently, often showed filaments of streptothrix growing out of the borders of the tissue mass. The rapid growths of *Bacillus subtilis* and molds began from the water of condensation and extended upward. These facts indicate that the organisms were within the lung proper.

A striking feature is the great similarity of the type of organisms encountered in the various species. Streptothrix appeared 87 times, *Bacillus subtilis* 41, molds 25. Practically all the organisms are spore-bearers, particularly abundant in hay and straw from which they probably originated. This would account for the larger number gaining access to the respiratory tract of herbivorous animals and explain their small numbers in the mouse and rat. The general characters of the streptothrix from the lungs of the animals resemble those obtained from hay and straw. The flora of the lungs of the mouse could be influenced markedly by varying the immediate environment. Mice under ordinary conditions showed a moderate number of organisms within the lungs. The number could be increased until they approximated those found in the guinea-pig or rabbit under normal conditions by subjecting them to the usual environment of the latter species. From the data presented it is obvious that the lung is readily invaded by air-borne organisms. It seems reasonable to assume that the spores of the various organisms which abound in dry vegetable matter are taken into the

respiratory tract with each inspiration. During deeper breathing a number must reach the small bronchioles and alveoli.

The bronchial lymph-nodes of all guinea-pigs examined developed, in  $66\frac{2}{3}\%$  of the tubes, organisms similar to those obtained from the lungs. The organisms are nonpathogenic when injected subcutaneously. The spores then are comparatively inert and are taken care of by the same mechanism that functions in the case of coal dust and other inert matter. This seems to explain their presence in the bronchial lymph-nodes. The observations have some practical bearing in the study of respiratory disease, especially in species like the rabbit and guinea-pig. By withholding spore-bearing substances, such as hay and straw, it is possible to cut down the number of contaminating organisms.

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**An Epidemiologic Study of Rhinitis (Coryza) in Calves with Special Reference to Pneumonia.**

*F. S. Jones and Ralph B. Little, J. Exper. Med., 36:273, Sept. 1, 1922.*

The authors have been able, by microscopic and bacteriologic examination of the nasal exudate of a group of calves subject to coryza and pneumonia, to throw light on the means of dissemination of the infective virus and the method by which it may be maintained over considerable periods. Previous studies had resulted in the isolation of 2 immunologically distinct strains of *Bacillus bovisepcticus*, Groups I and II. Sterile swabs were used to obtain the nasal secretions, films being prepared immediately before washing in sterile saline. The washings were then cultured on blood agar plates. The hemolytic properties of Type I rendered its recognition easy. Colonies surrounded by the narrow zone of hemolysis were subcultured. If, on microscopic examination, the subculture resembled *Bacillus bovisepcticus*, transfers were made to plain agar. Growth from the latter was suspended in normal saline and tested against Group I antiserum. When a culture agglutinated with the serum the fermentation characters were defined. Bile solubility afforded a ready method of distinguishing the members of Group II.

Of 32 calves in one barn, exposed to the epidemic disease under investigation, 10 developed clinical manifestations; 2 died of diffuse pneumonia. From these, *bovisepcticus* Group I organisms were obtained at autopsy. Four affected with pneumonia and 8 others which failed to show symptoms of pneumonia developed purulent rhinitis. From the nasal exudate of these cases Group I organisms were cultivated. The characteristic rhinitis was reproduced experimentally by brushing the nasal mucosa with a swab dipped in culture. Certain of the animals which suffered from the spontaneous rhinitis continued to carry the organisms in the nasal passages for as long as 121 days. It is of interest that both types of organisms may exist in specific instances on the nasal mucosa. After the first outbreak had subsided practically all calves introduced into this barn developed a milder type of rhinitis associated with organisms of Group II *bovisepcticus*; 25% of such calves continued to carry the organism on the nasal mucosa for periods of 50-73 days. It was possible to induce nasal infection in calves with pure cultures of this organism.

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**Types of Pneumococci in Italy.**

*Tomasso Pontano, Ann. d'igiene, Rome, 32:525, July, 1922.*

The author offers some brief considerations on the immunitary and serologic phenomena that distinguish the group of pneumococci in 4 types, studying the action of the various types predominating in Italy in 1920-21, using hemoculture, lung puncture, culture of pus from empyema, from pneumococcic arthritis and from the fluid of meningeal complications, for the isolation of the germs. For identification he adopted the specific agglutinating serums furnished by the Rockefeller Institute and by the Board of Health of New York. Among the stocks isolated there was a clear predominance of Type I (51%), after which came Type II (22%), then Type III (11%) and finally Type IV (4%). The percentage figures agree with results published in America; they differ markedly from those obtained by the French investigators. In the mortality percentages, Type III predominates, as the most virulent. In cured cases the variety of type did not seem to show any appreciable difference in the course of the disease. Pleural complications are determined more frequently by Type I; articular complications by Types I and III; to Type IV was due 1 case of primary diplococcic meningitis.

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**The Action of the Pneumococcus on Aromatic Amino-Bodies. A Differential Medium.**

*W. J. Penfold, M. J. Australia, Sydney, 2:120, July 29, 1922.*

All pneumococci, and probably all streptococci, acted on certain aromatic amines, notably anilin, benzidin and the toluidins, producing pigment. The pigments were probably due to the oxidation of the amino-bodies by the peroxid produced by these organisms. This anilin pigment production served to separate the pneumococcus and streptococcus from the great majority of pathogenic organisms. It is possible that it might profitably be applied in field work for the detection of both the anilin pigment-forming and the anilin nonpigment-forming bacteria. Benzidin was the best of the aromatic amines for the purposes of this test; 18 c.c. of nutrient agar, 1 c.c. citrated horse blood and 1 c.c. 0.5% benzidin solution constituted an excellent medium for obtaining this reaction.

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**Rabbit Septicemia Bacillus, Types D and G, in Normal Rabbits.**

*Paul H. De Kruif, J. Exper. Med., 36:309, Sept. 1, 1922.*

In preparation for experiments on the epidemiology of rabbit septicemia there was occasion to examine, bacteriologically, the nasal mucosa of normal stock rabbits. Of the first series of 29 animals so examined, 15 were found to harbor rabbit septicemia bacilli, Type D, in great abundance. In the same series of 29 animals, 4 nasal swabs yielded plates heavily seeded with colonies identical with the mutant G form of rabbit septicemia bacillus. As with the mutant G organisms described in previous publications, these 4 cultures were likewise found to be

avirulent. The Type D organisms, however, despite their failure to cause fatal damage in their own host, were shown to possess the typical high virulence characteristic of this type, when injected intrapleurally into young rabbits. Rabbits which are carriers of Type D or G possess a definite amount of immune agglutinins, as evidenced by test of their serum against microbe G at pH 7.1. Rabbits free from infection with these organisms invariably have yielded a serum which fails to agglutinate Type G completely in 1:10 or higher dilutions.

These findings are important in that they demonstrate (1) that the carrier condition is associated with evidence of immunity, as determined by the presence of definite amounts of agglutinins in the blood; (2) that the serum of any rabbit, taken at random from normal stock, is not to be considered normal so far as the rabbit septicemia bacillus is concerned.

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**Studies of Hemolytic Staphylococci. Hemolytic Activity. Biochemic Reactions. Serologic Reactions.**

*Lois A. Julianelle, J. Infect. Dis., 31:256, Sept., 1922.*

Every strain of staphylococcus is definitely hemolytic but the point investigated in this work was to determine the cause of the hemolytic activity. Staphylococci were found to produce a hemolytic substance in broth which appears on the sixth day, reaches a maximum at the ninth or tenth day and disappears between the thirteenth and sixteenth day. This hemolytic substance is thermolabile, is unaffected by the presence of carbohydrates, and appears to be associated with proteolysis and possibly autolysis. All cultures of staphylococci isolated during the course of the investigation appear to be hemolytic, only the time of its manifestation is in some cases considerably delayed. Hemolytic cultures do not lose their hemolytic powers by continued transplantations into blood-free mediums for a period of more than 4 months. Hemolytic activity shows no relationship to any of the biochemic reactions studied. Very little work has been done on the complement fixation of staphylococci, but the author found that the organisms do fix complement specifically. He does not feel that they can be classified by such an expedient. Agglutination and absorption tests were studied on 25 strains, and these fell into 3 groups, with 2 ill-defined subgroups. These groups appear to bear no relation to virulent hemolysis or biochemic activity. Group 1 apparently includes the light pigmented and less virulent strains. These groups may account for the variations experienced in the use of serum and vaccines.

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**Variation Phenomena in Streptococci, with Special Reference to Colony Form, Hemolysin-Production and Virulence.**

*Mary L. Cowan, Brit. J. Exper. Path., London, 3:187, Aug., 1922.*

This work was undertaken in an attempt to obtain evidence for or against the possibility of classifying streptococci by means of agglutination. Broth cultures of several strains of streptococci, 8 hemolytic and 2 nonhemolytic, were plated. From the plates numerous colonies were picked to serum broth and incubated for 24 hours. From the tube



showing the most even turbidity, and that with least, plates were again made. The most even and the most irregular colonies were picked to serum broth. These operations were repeated over a period of about 4 months before a definite difference could be relied upon to appear in every culture. Each strain worked with finally yielded 2 definite types of organisms—"roughs" and "smooths." The author found that the "smooths" grow with even turbidity in broth, and form bluish translucent colonies with even outline and a very finely granular surface on agar. The "roughs" grow as a precipitate in broth, and on agar have white, more opaque, coarsely granular colonies with irregular outlines, often appearing as a tangled mass of 1 long chain of organisms. Microscopically the "roughs" showed more clumps and much longer chains than the "smooths," also more variation in size with a distinct tendency to be larger. Some of the "rough" forms also had a mucous growth in broth. No capsules were demonstrated. Inoculation of mice and rabbits with the "rough" or avirulent type appeared to afford considerable protection against the "smooth" or highly virulent form. Hemolysin production the author found to be not a dominating factor in streptococcal virulence.

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**The Tetanus Bacillus as an Intestinal Saprophyte in Man.**

*Carl Tenbroeck and Johannes H. Bauer, J. Exper. Med., 36:261, Sept. 1, 1922.*

The authors report the results of examination of the feces of 78 individuals, all male Chinese of the poorer class with the exception of 1 American. Evidence is presented that tetanus bacilli are normal inhabitants of the intestinal tracts of certain individuals. For the bacteriologic studies, a tube containing a 10% suspension of feces in sterile saline was immersed in a water bath at 80° C. and kept there for 20 minutes to destroy the nonspore-bearing organisms, after which 1 c.c. of the suspension was transferred to sugar-free bouillon containing a fragment of sterile rabbit kidney or spleen in a fermentation tube as recommended by Smith for the cultivation of anaërobes. After 4 days incubation, films were made from the sediment and searched for terminal round spore-bearing forms characteristic of tetanus bacilli. Confirmatory mouse inoculations were then done to demonstrate the presence of a spasm-producing toxin, which could be neutralized by tetanus antitoxin. The injection of mixed cultures is not a reliable method for detection of tetanus bacilli, as the extraneous organisms interfere with the production of, or destroy tetanus toxin. For this reason great care was exercised to obtain pure cultures by repeated plating and transplanting.

Of the 78 stools examined, 27 or 34.7% yielded organisms which in their morphology and toxin-producing properties were tetanus bacilli. The results show that one-third of the male population in the vicinity of Peking carries tetanus bacilli in the digestive tract and that the bacilli probably multiply in the intestines. The growth of this bacillus in the digestive tract is shown by its presence in individuals who have been on a practically sterile diet for a month or more, and by the elimination of several million spores of this organism in a single stool. Man thus plays a large rôle in the distribution of the bacillus, for it is not uncommon to see human feces deposited in the streets of Peking, and human

feces are used to fertilize the fields. However, foreign physicians in China see few adult tetanus cases due, possibly, to the fact that carrying the organisms in the digestive tract for some time produces a relative immunity to this disease.

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(1d—171)

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**Studies on the Effect of Surface Tension of the Culture Medium on the Bacillus Tuberculosis.**

*P. Y. Chang, China M. J., Shanghai, 36:311, July, 1922.*

The work reported in this paper is a continuation of the study conducted by W. P. Larson on the effect of surface tension of the culture medium on the growth of bacteria. He found that the surface tension of ordinary liquid mediums could be reduced by the addition of certain soap solutions. With the lowering of the surface tension he was able to change the usual characters of the growth of pellicle-bearing organisms, thus, *Bacillus subtilis* and *Bacillus tuberculosis* grow down in the body of the mediums. The cause of the pellicle formation on such organisms as tubercle bacilli was considered to be their vital demand for oxygen. This theory can safely be ruled out inasmuch as tubercle bacilli could grow, and grew even better, in mediums or at the bottom of a medium when the surface tension was lowered. A more striking fact to disprove the oxygen demand theory is that a lowering of the surface tension of the medium does not create an increase of oxygen absorption in the medium.

Experiments were made using potassium rescinoleate, sodium rescinoleate, potassium oleate, sodium chlorid, sodium oleate, potassium palmate, sodium palmate, potassium stearate and sodium stearate. The potassium soaps apparently have a specific wetting effect upon the membrane since the potassium soaps cause the organism to grow down in the medium at a much higher surface tension than do the sodium soaps. The selective zone at or near the surface of the medium is probably more desirable for the development of bacteria in that in this zone the conditions of wetting are better, and hence the possibility of the organisms getting nutritive material more readily. The castor oil soaps have been found to be the best surface tension reducing agents since they more readily fulfil the requirements than do the other soaps, although they are by no means ideal. By comparison with other bacteria it is believed that the tubercle bacillus raises the surface tension of the medium as the growth and development of the culture progress. The pathogenicity of the strains used in these experiments could be attenuated, if not completely removed, by prolonged growth in a medium of low surface tension.

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(1d—172)

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**Studies in Tuberculosis. VII. Experiments in Reinfection with Acid-Fast Bacteria from Examinations of the Eye.**

*L. Igersheimer and H. Schlossberger, Deutsch. med. Wchnschr., Leipzig, 48:1001, July 28, 1922.*

The method of the experiments was as follows: Normal animals were given a preliminary subcutaneous treatment with original strains, passage strains or true bacilli of tuberculosis and after 4-6 weeks they

were again inoculated in the anterior chamber of the eye with original strain, passage strain or true bacilli of tuberculosis. Nine groups arose, in considering all the possibilities of variation. The essential result of the experiments was that animals that were given preliminary treatment with passage strains behaved in the same way toward superinfection with the human type as did animals that were given preliminary treatment with the human type of *B. tuberculosis*. The preliminary treatment with original strains had in general no effect on the course of the superinfection with virulent strains.

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(1d—173)

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**The Question of Increasing the Virulence of Acid-Fast Saprophytes by Passage through Animals.**

*B. Heymann and W. Strauss, Deutsch. med. Wchnschr., Leipsic, 48:999, July 28, 1922.*

Kolle, Schlossberger and Pfannenstiel, in experimental attempts to increase the virulence of acid-fast saprophytes by passage through animals, found that animals after being infected with strains that had been passed through other animals almost always died spontaneously and that the oftener the strains had been passed through animals the more the picture resembled that produced by the administration of true tubercle bacilli. The pathologic changes in these animals showed the picture of a true disseminated tuberculosis with nodule formation and central foci of caseation.

The author examined 5 cases that had been infected with saprophytes of Schlossberger's original strains and 10 with strains after passage. The Frankfurt original cultures produced in most of the animals no changes or only such slight ones and so little characteristic that it did not seem worth while to make any further inoculations with parts of organs. The Frankfurt cultures after animal passage in doses of 0.00001 mg. without exception produced intense tuberculosis; the tuberculin reaction was always positive. The further inoculation with pathologic organs of animals inoculated with Frankfurt original strains did not cause any perceptible changes, except with the Arloing strain, which did not produce severe changes. The tuberculin reaction was always negative. Passage cultures made by the author in Berlin by inoculating animals with 3 different Frankfurt original cultures, the animals being killed after 4-12 weeks in spite of equally high dosage, did not produce more pronounced pathologic changes than the original cultures. Here too the tuberculin reaction was always negative. Hence the increased virulence observed by Kolle and his colleagues was not observed by the author in a single case either in immediate animal passage or in the inoculation of pure cultures of passage strains. It was also found that only the Frankfurt original strain and its Berlin passage cultures gave a reaction with chicken tubercle bacilli, while on the other hand, only the Frankfurt passage strain reacted with Koch's tuberculin. The Frankfurt passage strains, therefore, seem to have been pure cultures of true tubercle bacilli. The animals may have had a house infection during the course of the experiments, probably from a patient with tuberculosis who scattered bacilli.

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**The Increase of Virulence of Acid-Fast Saprophytes by Animal Passage.**

*Bruno Lange, Deutsch. med. Wchnschr., Leipsic, 48:1000, July 28, 1922.*

The testing of the virulence of passage strains and original strains at the Frankfurt Institute has shown definitely that the passage strains were true tubercle bacilli and not transition forms from acid-fast saprophytes to tubercle bacilli. It is probable that in the experiments of Kolle, Schlossberger and Pfannenstiel, there was a complicating infection with true tubercle bacilli. There was no increase of virulence in acid-fast saprophytes after a long sojourn in the body of warm-blooded animals.

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(1d—175)

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**Retention of Virulence of a Microörganism Kept in a Sealed Culture.**

*W. F. Harvey and K. R. K. Iyengar, Indian J. M. Res., Calcutta, 10:190, July, 1922.*

It has previously been established that an organism such as that of fowl cholera retained its original virulence without animal subpassage when subcultured weekly on a blood-agar medium for as long as 12 months, at least. This organism, however, lost enormously in virulence when subcultured weekly on ordinary nutrient agar medium.

The authors recently tested the virulence of the same strain of the same organism, after it had remained for 12 months as a growth, without subculture, at room temperature, in a sealed test-tube. Exact doses of the organism were administered intravenously to pigeons. It was found that the full virulence of the fowl cholera culture was maintained under these conditions. Varying doses of the original culture resulted in death within 24 hours, in the case of all but 1 pigeon, which survived. The sealed culture, after 12 months, was lethal within 24 hours in 7 cases, within 48 hours in 2 cases, and within 72 hours in 1 case.

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**The Number of Microörganisms as Related to the Result of Disinfection. Method of Experimental Disinfection.**

*Bruno Lange, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:92, May 24, 1922.*

It was frequently noticed in experiments on bactericidal factors (high temperature, lack of food, exposure to light, chemical methods) that the action of the destructive agent is more potent on dilute suspensions than on concentrated suspension of bacteria. Not all bacteria are killed with the same rapidity, some being destroyed quickly, others more slowly, which is attributed to variability in resistance and to variable distribution of the bacteria in the fluid.

The author sought to determine how the lowered disinfectant activity upon a naturally resistant culture is influenced (1) by a great number of bacteria; (2) by the artificial increase of resistance through

incidental action of the medium of suspension, and (3) with chemical disinfectants, by dilution.

From the experiments with heat it may be concluded that only in highly dilute suspensions is the lethal time regularly but slightly increased as the concentration is increased. In highly concentrated suspensions the result of disinfection, as compared with lower concentrations, is much worse than would be expected from the number of bacteria. The result is not entirely dependent upon the resistance of the microorganisms, for poor results follow the addition of killed or slightly resistant bacteria. The greater the number of bacteria in a suspension, the more chances are there that certain resistance-increasing conditions will influence many of them, and the more abundant the culture, the more likely is it that some of the bacteria will survive and be transferred to the next cultures.

The action of cresol on highly concentrated bacterial suspensions can be ascribed partly to the dilution of the disinfectant. For practical purposes disinfection experiments should be carried out in the following way. The maximum bacterial suspension should contain a drop of a thick bacterial mixture in a few cubic centimeters of fluid. Pieces of batiste should be treated with a drop of this suspension and immersed in a few cubic centimeters of the disinfectant fluid. Greater bacterial concentrations have no advantages over this suspension, as the slight diminution of the disinfectant activity depends only partly upon the variability of resistance of certain bacteria. In order to obtain comparable results, the number of bacteria in each test must be about equal.

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(1d—177)

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**The Relative Effect of Certain Triphenylmethane Dyes upon the Growth of Bacilli of the Colon Group in Lactose Broth and Lactose Bile.**

*C.-E. A. Winslow and A. F. Dolloff, J. Infect. Dis., 6: 302, Sept., 1922.*

The 3 dyes chosen were gentian violet, rosolic acid and brilliant green; 5 organisms were used for the test, e. g. *Bacterium acidilactici*, *Bacterium aërogenes*, *Bacterium coli* (2 strains) and *Bacterium pneumoniae*. It was found that in lactose broth rosolic acid is inhibitive in a concentration of 1:1000 for all organisms studied; and in the lactose bile medium the action of this dye is exactly the same. Gentian violet is 5-50 times as toxic as rosolic acid in the broth medium, the individual organisms showing marked variations in susceptibility. In the bile salt medium the toxicity of gentian violet is exactly the same as that of rosolic acid, 1:1000 being inhibitive. With brilliant green startling differences appear. This dye inhibits the organism studied in concentrations between 1:100,000 and 1:1,000,000 in the broth medium, the strains of *B. aërogenes* type being more resistant than those of *B. coli* type. In the presence of the bile salt, however, the extreme toxicity of brilliant green wholly disappears, *B. aërogenes* and *B. pneumoniae* growing even in a concentration of 1:500. These facts are important in relation to the choice of mediums for selective cultivation based on the use of the triphenylmethane dyes.



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**Mycetes in Human Beings and Animals. Botanic Study of the Dermatomycoses.**

*Gino Pollacci, Riv. d. biol., Rome, 4:313, May-June, 1922.*

The author studies 2 species of Mycetes isolated from osteoperiosteocutaneous gummatous growths on the thorax of a girl of 13 years, partly intrathoracic, which opened externally by fistulas terminating in cutaneous ulcerations, with softened and uncovered edges. There was extensive subcutaneous infiltration, and elimination of masses of suppurative, necrotic tissue. The condition was markedly ameliorated following the administration of iodid of potassium.

Two different species of Hyphomycetes were isolated. The first, probably developing casually as a saprophyte in the gummas of the subject without participating in the determination of the morbid process, was of the genus *Torula*, and is named by the author *Torula bestae*. In the culture mediums that he adopted (broth 1000 gm., peptone 10 gm., sodium chlorid 5 gm., agar 15 gm., to which is added after boiling, filtering, neutralizing, and again boiling for a half hour, 70 gm. glucose), at a temperature of 15°-20° C., the fungus forms on the fourth day flakes of shining hyphae, on the seventh day colonies tending to a rose color; on the fourteenth day, these appear as a dull rose color becoming hazel, and round spores appear; on the twentieth day the colonies form a continuous coating of a bright hazel color. When cultured in microculture in the dark, at 20° C., and observed under the microscope, the fungus showed minutely divided hyphae, first transparent, then pale rose, finally hazel, interlacing after a few days to form abundant conidiophores closely resembling the hyphae; these carried on their extremities round spores (2-6) disposed in easily detachable chains.

The second species isolated was considered by the author to be the specific agent of the lesions presented by the patient (which were reproduced in mice by inoculation). This was a trichosporon, called by the author *Trichosporon mantegazzae*. Cultured in the medium described, there are formed on the fifth day hyphae of a grayish color, united in small round colonies, which turn grayish-green towards the tenth day; on the twentieth day they are black and form a curly cloak that covers the entire surface of the culture mediums; on the thirtieth day they are a dense black crust. In microculture, there appear round spores, without division, of a diameter of 6-7 microns; they grow easily, producing a transparent filament with division, of rapid growth, brownish in color and ramifying, producing a thick, dark brown reticulum; the conidiophores consist of filaments (these form in the oldest parts of the colonies) which bear many spores, inserted without order in the walls and at the apex. The older vegetative hyphae, becoming dusky and thick, form numerous divisions; some swell, become barrel-shaped, and are transformed into chlamydospores, very abundant in the old colonies and germinating readily. The trichosporon described is quite similar to various species of *Sporotrichum* but is differentiated from each of these by some characteristic of its own. The species of *Trichosporon* here described is also found, according to the author, on vegetables, probably as a saprophyte. Man presumably contracts trichosporosis mainly from plants; possibly at first the mycetes is incapable of parasitic life, habituating itself little by little to the human medium till it can live on it, first as a saprophyte and finally as a disease agent.

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**A New Variety of Streptothrix Cultivated from Mycetoma of the Leg.**

*J. W. Cornwall and H. M. Lafrenais, Indian J. M. Res., Calcutta, 10: 239, July, 1922.*

This organism was both aërobic and anaërobic. It grew upon most of the usual mediums, but not upon saline mediums for fungi and plants in the absence of protein and carbohydrate, and it failed to grow on fluid extract of the local soil, or in the soil itself. It is probably, therefore, not an organism whose natural habitat is the soil, and which enters an abrasion on the patient's leg. The earliest growth on both solid and fluid mediums consisted in long, hyphal filaments with lateral buds or branches at irregular intervals. The branching was not dichotomous, and did not follow any system. The filaments were not septate. The walls of the filaments were thin and difficult to distinguish from the protoplasmic contents. In fluid mediums filamentous form persisted; in solid mediums the hyphal walls soon disappeared, freeing the contained rods and rounded grains, which were of variable form. The protruding ends of the filaments of young, round colonies were sometimes clubbed. In mediums poor in nutrition the filamentous type persisted; in the nutrient mediums rod and coccoid forms appeared rapidly. A mixture of salts with a small quantity of casein caused arthrospores to be produced much more abundantly than did any other medium.

The organism differs from all varieties of *Streptothrix madurae* so far described by being relatively acid-fast as well as alcohol-fast, especially during the first few weeks of the culture. It is not known whether or not the loss of acid-fastness by a pathogenic streptothrix leads to a loss of its pathogenicity, by exposing it to the defensive mechanism of the host, but it is probable that the acid-fastness is not essential to the life and metabolic activity of the organism.

This organism belongs to the class, Schizomycetes; order, (4) Eubacteriales; family, (8) Mycobacteriaceae; genus, (1) Actinomyces. The species is not yet determined. Inoculations of the streptothrix into animals caused the formation of scabs at the point of inoculation; these gradually disappeared.

So far streptothricial infection has not proved amenable to treatment by drugs. Potassium iodid has been used with variable success. It is of no use in mycetoma, in which the usual treatment is amputation. Possibly, in streptothricosis, as in leprosy and tuberculosis, treatment with vegetable and animal oils may prove applicable. In these experiments the streptothrix failed to grow in mediums to which sodium morrhuate or sodium gynocardate had been added, except in high dilution. Little is known of the influence on mycetoma of infecting streptothrix vaccine, combined with a vaccine prepared from the pyogenic organism secondarily infecting the sinuses.

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**An Eruptive Disease of the Goat Occurring in Greece.**

*Georges Blanc, C. Mélanidi and J. Caminopetros, Ann. de l'Inst. Pasteur, Paris, 36: 614, Aug., 1922.*

The disease discussed appears as pustules and crusts about and within the mouth of the affected goats. The course is mild and cure occurs spontaneously in 2 to 3 weeks. By inoculating an emulsion of the

crusts in normal saline solution upon the scarified skin, the typical lesions were readily reproduced. Laboratory animals other than the sheep are resistant. The virus is preserved well in glycerin, still better by drying. The dried crusts are very virulent. The virus is filterable. Sheep inoculated with the virus are not rendered immune to ovinia or vaccinia. Sheep inoculated upon or under the skin with a large dose (103 gm. of the tissue) of ovinia are not rendered immune to the virus examined nor is such immunity conferred by inoculation on the skin with vaccinia. Inoculations on the cornea and conjunctiva produce specific immunity. This fact shows that the infection described is quite distinct from ovinia and vaccinia, though, like these diseases, it most readily affects the ovine species. It is the same as that observed by Zeller in Southwest Africa. It is probably also identical with Aynaud's ovine pustular stomatitis.

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**Serologic Researches on Protozoa. I. Morphology and Serologic Properties of Prowazekia (Bodo) Edax.**

*Ludwik Anigstein, J. Trop. Med. & Hyg., London, 25:241, Aug. 1, 1922.*

The flagellate used in this research is the same as the Bodo edax of Kühn, or Prowazekia (Bodo) edax. After having obtained a pure strain of Prowazekia, it was necessary to bring the culture up to the "mixed pure culture," feeding the flagellates with a single type of bacteria. In order to have a very large amount of flagellates, the author used 1% agar plates, which he covered with a thin layer of 1% peptone water or 5% broth. One drop of bacterial emulsion was added to each plate, then put for 24 hours in an incubator (28° C.) after which 1 loopful of flagellates was added. For this purpose, the pure strain, strain F, was cultivated with the following bacteria: *Bacillus proteus* X 19, *B. prodigiosus*, *B. coli*, *Staphylococcus albus*, *Sarcina lutea*. Only after a long series of inoculations from plates on fresh mediums, containing a pure culture of the special bacterium, it was possible to obtain a "mixed pure culture."

A specific immune serum was obtained both from rabbits and frogs by injections of Prowazekia plus *B. coli*, *B. prodigiosus* and *Staphylococcus albus*. The experiments to find lytic bodies in the immune serum against Prowazekia gave a negative result. A table shows that the agglutination of flagellates appears during the first minute of their contact with the specific serum. In the serum dilution of 1:1600 a weak agglutination appears only after 30 min. During the whole course of agglutination, the flagellates are in a state of active movement, so that the clumps are swimming about. The formed agglomerations do not dissolve as do agglutinated trypanosomes or amebas, but increase in size because of gluing to them of other flagellates. In these tests specific serum from one of the rabbits was used. The agglutination test with emulsions of killed Prowazekia gave a negative result. From one of the frogs a specific serum was obtained which agglutinated Prowazekia, but only up to the dilution of 1:500 after 1 hour.

Tables are given showing the standardization of antigen and complement fixation with the immune serum against Prowazekia plus *B. prodigiosus* with the antigen Prowazekia *staphylococcus* and the antigen

staphylococcus. The results of these tests indicate the existence in the immune serum of antibodies, fixating the complement in the presence of *P. edax*. This serum does not contain antibodies against the non-specific bacterial part of antigen, namely, against staphylococcus, notwithstanding the fact that they are employed in a double dose. Another table shows the results of a series of experiments with strictly homologous antigen, i.e. with *P. edax* plus *B. prodigiosus*. The results indicate that the complement fixation is specific for *Prowazekia* in presence of immune serum. The inhibition of hemolysis appears equally in the series, where *B. prodigiosus* only serves as antigen; it indicates that the immune serum contains also complement fixating antibodies against the bacteria with which the flagellates were cultivated. The inhibition of hemolysis in tubes containing double antigen is stronger than in tubes containing bacterial antigen only.

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**A Note on Bodies Observed in *Cimex Rotundatus* Linné Collected in a Kala-Azar Infected Area in Assam.**

*Helen A. Adie, Indian J. M. Res., Calcutta, 10:236, July, 1922.*

In a previous article parasites were described which were found in the salivary glands and ducts of *Cimex rotundatus* collected from the bed of a patient suspected to have kala-azar. Dissection of the insects revealed the parasites, which were leaving the glands in clusters. These clusters broke up after they were free from the gland. Single bodies were also seen. The parasites were small, oval, and non-flagellated. Many intracellular forms were observed in the intestines, and numerous freed forms outside the cells. The ovaries were infected.

Stained specimens presented various forms: Some had blue-stained cytoplasm and a definite red-stained nucleus. These were in clusters. Dividing forms were observed. The parasites varied in size, shape and nuclear structure. Some were large, round forms, with a macronucleus stained red, and a definite micronucleus stained purple. The cytoplasm stained blue, and was vacuolated. Some of the forms were oval, and had a blue-stained cytoplasm with a single nucleus. Many of these were apparently enclosed in an unstained area; possibly this was due to faulty technic. It may be that the unstained area represented a capsule; the different staining reactions may also be due to the stage of maturity of the parasites. Some of the small, oval forms contained 2 nuclei, but as a rule only 1 was found.

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**A Simplified Method for the Cultivation of *Plasmodium Falciparum* in Vitro.**

*J. A. Sinton, Indian J. M. Res., Calcutta, 10:203, July, 1922.*

In order to render the cultural diagnosis of latent malaria easier, a simplified technic was devised, by which it is possible to grow parasites in a few drops of blood obtained from the finger. A special culture tube was devised in which a few drops of blood could be taken, defibrinated and cultured, without the need of transference. The tube has a chamber with a flat bottom at its lower extremity. The reason

for this is that the best growth of malarial parasites is in the surface layers of the deposit of red blood-cells. The flat bottom increases the area of the layers, with a minimum amount of blood. The parasites require a layer of serum above them at least 12 mm. deep, and grow best with a layer 24-48 mm. deep. A maximum depth of serum with a minimum of blood is obtained by means of a narrow stem, between the flat chamber and the main tube, which is of larger bore. This stem also holds very little air, especially after it has been heated before sealing the tube, so a partially anaërobic condition is obtained. The stem is further narrowed where it joins the upper tube, to facilitate sealing it off. Two depressions are made just above this point, to prevent the glass beads, which are inserted into the larger tube to aid in defibrination, from blocking the entrance to the stem. The high temperature used in shaping the tube sterilizes it, and if the ends of the capillary tubes are sealed off immediately they remain ready for use at any time.

Ascitic fluid from the malarial patient is drawn off into sterile flasks. To each flask, containing 100 c.c. blood, is added 1.5-2 c.c. sterile 50% solution of dextrose. The flasks are heated for half an hour at 56° C., to kill the complement. Sinton has found hydrocele fluid as effective as ascitic fluid. The fluid may be kept in Wright capsules. The capillary end of the tube and the end of the Wright capsule are sterilized and the latter is broken. The upper end of the tube is inserted into the capsule, and the dextrose allowed to enter by capillary attraction until the upper tube is about two-thirds full. The finger is pricked and 5-10 large drops of blood are run in, above the fluid. The lower chamber is heated and the capillary tube below it sealed off. The tube is shaken until the blood is defibrinated by the beads. It is then swung rapidly, to drive the blood and fluid into the lower chamber and the stem, where it must form a solid column. The top of the stem is then sealed off. The tube is placed upright in a tray of plasticin and incubated. The culture to be tested is later pipetted off and the tube resealed. Various incubation temperatures have been employed. The optimum temperature for growth is about 37° C., or slightly lower.

It was possible, by this method, to cause the small ring forms of *Plasmodium falciparum* to sporulate. In one case growth apparently went on to the third generation. The first 2 specimens of *P. vivax* tested developed until the parasites were three-quarters grown, but degenerated before sporulation, possibly because they were cultured at a higher temperature (38°-41° C.). A culture at 35°-38° C. was successful.

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#### **A Case of Malaria Due to *Plasmodium Tenue* (Stephens).**

*J. A. Sinton, Indian J. M. Res., Calcutta, 10:215, July, 1922.*

It is still disputed whether *Plasmodium tenue* is a new species of malarial parasite. A heavily infected man, with a fever of 101.2° F., presented malaria parasites considered to be *Plasmodium falciparum*, and also forms corresponding to *P. tenue* (Stephens). The infection was double—slight infection with forms segmenting on the eighth, tenth, twelfth, etc., days, and a heavy infection with forms segmenting



on the alternate days. The temperature chart was quotidian, with slight tertian exacerbations.

The asexual forms of the parasite found in the peripheral blood included: (a) small ring or oval forms; (b) medium-sized, irregular, or oval-tailed forms; (c) pseudopodial or tenue forms; (d) large oval or polyhedral forms; (e) segmenting forms. The sexual forms consisted in crescentic gametocytes, such as those of *P. falciparum*.

Blood-smears were taken for 14 days. The tertian periodicity of the organism was apparent. Its ameboid character gradually increased until about 1 p. m. on the eighth, tenth, twelfth and fourteenth days, and then diminished, the parasites assuming the larger, oval, type, and pigment being developed just before they left the peripheral blood, preparatory to segmentation in the internal organs. The parasite differed from *P. vivax*, *P. malariae*, *P. falciparum*, and greatly resembled *P. immaculatum*. Sinton cannot determine whether *P. immaculatum* and *P. tenue* are identical, or whether *P. tenue* is a stage in the cycle of the subtertian *P. falciparum*.

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(1d—185)

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**Experiments on the Infectivity of Typhus Virus Contained in Lice. (*Pediculus Humanus* and *Pedicinus Longiceps*).**

*E. E. Atkin and the late A. Bacot, Brit. J. Exper. Path., London, 3: 196, Aug., 1922.*

The authors compared strains of typhus virus from Poland and from Ireland and found that the strains were apparently identical. Guinea-pigs which had survived attacks of typhus caused by inoculation with the Polish strain proved to be immune to the Irish virus. Guinea-pigs were infected by the injection of the emulsified alimentary tracts of human lice, which showed heavy infection with *Rickettsia prowazeki*. Some of these lice had been infected by feeding on typhus-infected monkeys, others by the rectal injection of platelet material obtained by the centrifugalization of blood from infected guinea-pigs. One monkey was infected with typhus by subcutaneous inoculation of infected monkey lice (*Pedicinus longiceps*), and a second was probably infected by the transference of living monkey lice from an infected monkey. Two attempts to infect guinea-pigs by the injection of infected monkey lice failed, as did attempts to infect monkeys and a guinea-pig by feeding infected human lice, and an attempt to infect a guinea-pig with the excreta taken from heavily infected human lice.

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**The Cultivation of *Spironema Duttoni* from a Case of Relapsing Fever.**

*I. J. Kligler, Brit. J. Exper. Path., London, 3: 215, Aug., 1922.*

The author reports what was apparently an atypical case of relapsing fever. Not until the patient's third attack, were successful blood cultures of the spirochetes made in buffered ascites and serum mediums and also in bouillon. These were kept over a month and passed to the third generation, when they were lost by a mould contamination. Transplants were made after 16 and 18 days respectively.

When the cultures were made, white rats were also inoculated intraperitoneally with the patient's blood. One to 2 days after the inoculation spirochetes appeared in the blood, increased in numbers for the next day or two and then disappeared, to reappear again after 2 days. No rat had more than 1 relapse. The strain was carried through 3 rat generations with the same results. It would seem that with the method described, it is possible to cultivate the spirochete of relapsing fever from the blood of patients and to maintain it under artificial cultivation for long periods.

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(1d—187)

**Leptospiras, Pathogenic and Nonpathogenic, Together with Some Observations on the Spirochetal Flora of Stagnant Fresh and Salt Water and the Mammalian Stomach.**

*Hideyo Noguchi, New York State J. Med., 22:426, Sept., 1922.*

The pathogenic varieties at present known are *Leptospira icterohaemorrhagiae*, from infectious jaundice, *L. hebdomadis* from seven-day fever, and *L. icteroides* from yellow fever, a nonfatal disease present in Japan, and *L. icteroides* from yellow fever. All 3 produce fever, hemorrhages, jaundice, and nephritis, individual symptoms differing in degree. Jaundice and nephritis are usually mild, and are often absent in *L. hebdomadis* infection. Jaundice, nephritis and fatty degeneration are more pronounced in the *icteroides* infection, while hemorrhage is predominant in the *icterohaemorrhagiae* infection. Serologic differentiation of seven-day fever and infectious jaundice and of infectious jaundice and yellow fever is possible by the Pfeiffer reaction, protection experiments, and to a certain extent by agglutination and complement fixation.

*L. hebdomadis* has been traced to field mice and *L. icterohaemorrhagiae* to wild rats, both organisms being apparently harmless parasites in the kidneys of these animals and probably scattered by means of the urine. The infection of man is believed to occur through exposure of the skin to the contaminated water of sewers and cesspools. Some authors do not exclude possible transmission by infected insects (mosquitoes, horse flies, etc.). During the past few years a number of spirochetes resembling the leptospiras more or less in morphology have been described by European investigators. Noguchi examined samples of stagnant water by the dark-field method, which revealed small numbers of leptospiras in all of the samples; in some samples the number was so small that repeated examinations were necessary in order to find even 1 organism. Both fresh and salt water contained organisms indistinguishable from *L. icterohaemorrhagiae*. Occasionally very short and minute (0.2 by 3-4 microns) and very heavy and long specimens (14-15 microns in length, maximum width 0.4 microns) were encountered. The spirals of the latter type were so tightly set together that the organisms appeared like a row of flat disks. These extremely small and large varieties are perhaps 2 different species, both differing from the *icterohaemorrhagiae* type.

In addition to these varieties, leptospira-like forms without any perceptible elementary spirals, apparently smooth-bodied organisms (?) were observed. Whether or not they were motile could not be determined. The movements of all the leptospiras found in water were

rather sluggish. Growth has been obtained of the water leptospiras in impure culture on regular leptospira medium, though with considerable difficulty. Inoculations of the leptospira water samples into guinea-pigs, white rats and mice have been repeatedly made, but no infection could be induced in the animals. Injections of cultures likewise proved to be harmless. The kidneys and liver of the inoculated rats were removed after 3 weeks and suspensions of these organisms injected into guinea-pigs with the hope that passage through rats might have enhanced the virulence of the organisms, but so far no positive results have been obtained. The water leptospiras appear to be nonpathogenic for guinea-pigs as well as rats. No attempts have yet been made to establish the immunologic relationships of the pathogenic and water varieties of leptospira.

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**Hypotonic Solutions in the Technic of the Morphologic Study of Microörganisms and the Staining of Spirochaeta Pallida.**

*Gianni Petragani, Policlinico (Med. Sect.), Rome, 29:434, Aug. 1, 1922.*

Whenever it is desired to make an investigation or a morphologic study of a microörganism present in small numbers in any material rich in saline and saccharine substances, and in organic substances in the colloid state, but poor in nucleated cells, it is useful to make a large drop preparation with successions of hypotonic baths, or with a distilled water bath. Also when it is necessary to make a smear preparation because the material is rich in cellular and bacterial elements, it is well to treat it with hypotonic solutions like the large drop preparations (purulent exudates, centrifuged serous exudates, excreta, feces, cultures in liquid mediums with abundant bacterial development). The treatment with hypotonic solutions becomes indispensable whenever the material to be examined is rich in saline and saccharine substances, or proteid substances in the colloid state, and whenever there is necessity for treatment with mordant stain for the investigation of eventual microörganisms, or elements not easily stainable with the simple aniline colors. Thus the preparation will be made by the large drop method in the exudate of syphilitic ulcers and for filtrates of infected tissues obtained by porcelain filtration with pathologic products triturated and emulsified in water; it will be, on the other hand, prepared by the very thin smear method for purulent exudates and blood of individuals affected with exanthematous diseases, yellow fever or epizoötic aphtha.

Technic: The preparations made with the large drop or smear methods by treating with hypotonic solutions and by staining with simple staining solutions are left to dry at room temperature for 12-24 hours; they are then immersed in the series of hypotonic solutions, in case the investigation is for a protozoan, a strongyloplasma, or cellular elements of delicate structure whose form is to be carefully preserved; but simply in distilled water, with the addition of a drop of oxygenated water, for each cubic centimeter, in case the investigation is for Spirochaeta, Schizomycetes, Hyphomycetes or Streptothrix.

The series of hypotonic baths may be: (1) distilled water with 0.6% NaCl; (2) distilled water plus 0.3% NaCl; (3) distilled water plus 1 drop of H<sub>2</sub>O<sub>2</sub> for each cubic centimeter. These solutions are used at the temperature of 30-37° C. or at room temperature. The preparation is held 5 minutes in the first solution, 5 in the second, 10-20 minutes, and even more, in the third; then dried and fixed in methyl alcohol, or in ethyl ana-ether-alcohol, or in the flame, stained with one of the many stains of bacteriology, washed under the current, and dried. When, on the other hand, it is desired to adopt for the preparation a process of staining by fixation, after the hypotonic bath, instead of the ordinary fixation in alcohol, the fixation is done with the liquid of Petraghani, by means of a very fine camel's hair brush, then stained with a solution of carbolfuchsin or its equivalent. This technic may be adopted for staining of *Spirochaeta pallida*; these are intensely colored in aniline red with great clearness. The cellular bodies that are eventually found take the stain more intensely in the nuclear than in the protoplasmic part and when including bacteria these are distinguished clearly by the brighter color they assume. The shades of the erythrocytes are slightly tinted, but this does not interfere with the view of the spirochetes that are found eventually under or over them because these are more intensely colored.

The author believes that the other methods, also, for the staining of the *Spirochaeta Schaudinn* may give better results, and can perhaps be used on large drop preparations (which greatly facilitates diagnosis), if the hypotonic solutions are first used on the dried preparation. The necessity for improving the technic of the investigation of the *Spirochaeta pallida*, especially in the early manifestations, is of the greatest importance to-day in view of the utility of the abortive treatment of syphilis, i.e. in the early period of the infection, in which there is still lacking the serologic proof.

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### **An Injection Method for Aiding in the Identification of Tapeworm Species.**

*Raphael Isaacs, J. Lab. & Clin. Med., 7:691, Aug., 1922.*

A simple method for visualizing the uterus in tapeworm proglottids consists in the injection of the canals with India ink. A hypodermic syringe (1-2 c.c.), fitted with a fine needle, is filled with India ink. The segment to be injected is held flat on a piece of glass by means of a wooden match stick or applicator, and the needle inserted into the substance of the fresh proglottid, near the lateral genital pore. With a little manipulation, one of the diverticula of the uterus is easily entered, and the ink readily fills the branches. Pressure between 2 glass slides brings out the details very clearly, and the sparsely branched organ of *Taenia solium* is easily differentiated from the more abundant ramifications of *Taenia saginata*. The method is also applicable to other cestodes, and may be used with preserved material. Permanent preparations may be made by preserving the flattened segment in 10% formaldehyd, dehydrating in alcohol, and, after clearing in xylol or carbolxylol, mounting in balsam.

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**A New Species: *Taenia Infantis*.**

*Juan Bacigalupo, Semana méd., Buenos Aires, 29:302, Aug. 10, 1922.*

The specimen was eliminated by a boy 5 years old. The worm was 30 cm. long, and was formed of rings with lateral genital pores, irregularly distributed. The first segments were wider than they were long, the median rings more or less square, and the terminal ones were longer than they were wide. The head was round, with 4 orifices and a double row of hooks; the neck was short and slightly narrower than the head. The eggs were round, and measured 35-40 microns in diameter. The specimen resembled *Taenia crassicollis*, but was not identical with it. It was assumed to be a new species and was given the name *Taenia infantis*. A month previous to the total elimination of the worm a portion 10 cm. long, with dark segments, was eliminated. The intestinal symptoms present at this time were treated with etheric extract of fern, resulting in the elimination of the entire worm. The manner of ingestion of the worm or egg could not be determined.

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**Note on the Value of a Tame Cow for Collecting the Blood-Sucking Diptera of a Locality.**

*W. S. Patton, Indian J. M. Res., Calcutta, 10:66, July, 1922.*

Patton found a tame white cow extremely useful in collecting blood-sucking Diptera of Madras. He was able to obtain all the specimens of this locality, including many Culicidae which would otherwise have been difficult to catch. He took the cow into the brush-wood, near water, especially at dusk. The flies settled freely upon her, and could be easily caught in a net. A tame cow is necessary for this purpose, for ordinary domestic cattle resent having a net brushed over them, and the application of test-tubes, and there is danger of breakage and of loss of specimens.

The blood-sucking and blood-feeding Diptera included various species of Nematocera, Brachycera, and Schizophora (muscidae).

**1e. IMMUNOLOGY, SEROLOGY AND HEMATOLOGY**

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**Chemical Changes of the Blood during Immunization.**

*G. L. Rohdenburg, O. F. Krehbiel and A. Bernhard, Am. J. M. Sc., 164:361, Sept., 1922.*

Authors' experiments show that during the process of immunization there occur disturbances of the total nitrogen content and total solids of the blood, as well as of the blood sugar and of the pH. None of these disturbances except those of the blood sugar and pH can be correlated with the development of antibodies. The repeated injection of a given antigen results in disturbance of both blood sugar and pH equilibrium until the point is reached where the organism has exhausted its antibody-producing powers against the specific antigen. After the



antibody-producing powers have reached this phase no further disturbance of blood sugar or pH equilibrium occurs until the organism has recovered, unless another antigen is used.

This principle is applied in a study of the reactions in animal tumors, and it is shown that there is no difference between the reaction of normal mice and rats and of those bearing tumors when injected with adrenalin or with heterologous protein. However, when homologous protein is injected a large majority of normal animals and animals bearing receding tumors react to the injection with a marked disturbance of the blood sugar equilibrium, while animals bearing spontaneous tumors or tumors which are progressively growing show either slight or no disturbance of blood sugar equilibrium.

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### **Biology of the Skin and Immunity.**

*P. H. van der Hoog, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:785, Aug. 19, 1922.*

The keratin and fatty layers of the healthy skin successfully protect the organism against chemical and mechanic injury, and also against unfavorable temperature and atmospheric conditions. The cutis and subcutis maintain the elasticity of the skin. The action of light on the organism depends upon the permeability of the skin, and upon the formation of pigment in the basal cells. The rôle of the skin in the elimination of toxins is of the greatest importance in immunity.

The skin presents allergic immunity, in contradistinction to the serum immunity found in tetanus and diphtheria. The processes which cause allergic changes in the body affect the skin (tuberculosis of the skin, syphilis, typhus fever). The more violent the cutaneous reaction, the less the internal organs are involved. The fact that burns affecting more than a third of the body surface are invariably fatal illustrates the importance of the skin in protecting the organs. The epidermis evidently contains protective substances which enter the circulation and thence reach the internal organs. Bloch is convinced that the lack of allergic cutaneous reactions is one of the causes of neurosyphilis. The spirochetes become localized in the nervous tissue before the protective substances of the skin can take effect. The fat-poor nerve tissue offers no resistance to the microorganisms, which penetrate to the brain.

Theoretically, any agent which artificially increases the allergic cutaneous reaction should be of therapeutic value in syphilis. It has been found that 1 c.c. of an isotonic solution of milk-albumin, injected subcutaneously, causes practically no tissue changes within 24 hours, while a fifth of this dose, injected into the corium, increases the number of leukocytes in the subcutaneous blood-vessels in 30 minutes to an hour. Not the substance injected but the method of administration (whether intracutaneous or subcutaneous) affects the reaction.

The process of immunity depends upon the phagocytic properties of the leukocytes, which are capable of absorbing bacterial and protein toxins and rendering them harmless, by means of the contained ferments. These ferments are not produced by the leukocytes themselves but by specific organs, and are furnished in an inactive form; when the necessity arises the activating substance, or phagokinase, is introduced

into the leukocytes, which are destroyed by the phagolytic process. It is the skin which furnishes this phagokinase. The intensity of its production is indicated by the opsonic index. Experiments have demonstrated the presence of phagokinase in the peripheral blood. Toxins due to the improper elimination, and resorption, of metabolic products, derived from the intestinal canal, may reach the basal cells, by way of the blood, and cause irritation which later leads to various skin diseases. Eczema has been attributed to this cause, though various exogenous irritants may also cause it. The external application of formol and the internal administration of urotropin have been observed to cause similar forms of eczema. It is still not known which endogenous substances, transmitted by the blood, are causative.

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**Observations in Nonspecific Immunity.**

*Paul F. Clark, C. E. Zellmer and H. W. Stone, J. Infect. Dis., 31:215, Sept., 1922.*

It has been shown from statistics that when people from rural communities are brought suddenly into close association with many persons, they exhibit a lower resistance to the ordinary communicable disease than do their city brethren. The most important factor in the greater resistance of city dwellers is an actual specific immunity acquired during the course of recovery from recognized cases of measles, whooping-cough, chicken-pox, and similar infections. The incidence of such acute diseases is higher in most parts of the United States among city children than among children in farming districts. This leads to the question whether a nonspecific immunity may be developed among the city dwellers because of the greater interchange of organisms and the higher incidence in general of communicable diseases in our cities. To investigate this question, twelve rabbits were selected, bled for a normal serum sample and placed in individual cages. One group was given series of vaccines, and called city dwellers. The vaccines were made from *Staphylococcus aureus*, *Streptococcus hemolyticus*, *Streptococcus viridans*, *Pneumococcus*, and another strain of *S. viridans*. The other rabbits were not vaccinated, but were kept under similar conditions, and were called country dwellers. The twelfth day after the last injection of the cocci, both the vaccinated and unvaccinated groups were injected intravenously with *Bacillus typhosus*. Two of the city dwellers were eliminated for other reasons, but within 15 hours after the second injection of *B. typhosus* all the country dwellers were dead, while the other 4 city dwellers were well and happy. Other animals were then obtained and used as country dwellers. The experiments were repeated, the primary antigen introduced in small daily doses and the secondary antigen by the intratracheal route, instead of intravenously, in an attempt to reproduce more nearly the conditions prevailing in the human body. By the intravenous injections of repeated doses of Gram positive cocci, then, rabbits are rendered more resistant to the injection of a totally unrelated organism, *B. typhosus*. This type of vaccination caused the rabbits to respond when inoculated with *B. typhosus*, by building up a higher concentration of agglutinins against this unrelated antigen than do normal

animals kept under the same living conditions. It seems probable that a similar nonspecific immunity may be built up in human city dwellers.

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**The Effect of Urea on the Immunologic Reaction.**

*Noble P. Sherwood, J. Infect. Dis., 31:252, Sept., 1922.*

Sherwood has studied the effect of urea on human, guinea-pig, dog and hog complement, and on normal dog antihuman hemolysins, and the effect of intravenous injections of urea and sodium chlorid, respectively, on rabbit complement and the leukocyte count. These observations were paralleled with blood-urea determinations. Urea solutions restrain the union of complement with the amboceptor-cell complex. The slowing effect varies for different complements ranging from permanent fixation for human complement to no appreciable effect for guinea-pig complement. In test-tube experiments it requires 10 times as much M/1 urea to inhibit rabbit, 7 times as much for hog complement and 10 times as much for dog complement, as it takes for human complement. Urea in salt solution in the concentrations used does not directly lysis red blood-cells or interfere with the union of amboceptor and red blood-cells. The intravenous injection of 2-6 c.c. M/1 NaCl produced a slight initial leukopenia followed by leukocytosis in rabbits. One injection gave an initial leukopenia lasting for 2 hours, followed by a return to normal. Repeated injections of M/1 urea solution were associated with a decrease in complement content. The slight rise in complement 2 hours after the initial injection was associated with apparent maximum activity on the part of the kidneys. Repeated injection of M/1 urea was associated with wide fluctuations in the leukocyte count, but on the whole produced noticeable leukopenia. One injection of 2 c.c. of M/1 urea gave an initial leukopenia followed by a marked leukocytosis, the blood count returning to normal within 3 hours, and remaining normal.

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**The Significance of Cholesterin in Infections.**

*Ernst Leupold and L. Bogendörfer, Deutsch. Arch. f. klin. Med., Leipsic, 140:28, July 25, 1922.*

Various authors have associated the frequency of degeneration of the suprarenal cortex and its poverty in cholesterin in the course of infectious-toxic diseases with a detoxicating action of the suprarenals. Stepp showed that in the majority of cases of febrile diseases the cholesterin content of the blood is decreased. The authors have examined Stepp's results in 20 cases of infectious diseases and determined the cholesterin colorimetrically by the method of Autenrieth and Funk. They regularly found a great decrease of the cholesterin in the blood which in the further course of the disease was generally overcome and often during convalescence gave way to hypercholesterinemia. As they found that the decrease of cholesterin was not caused by the fever in itself nor by insufficient nutrition they considered it proved that it was due to the action of a toxin. This suggested that in infection, cholesterin is used to bind the toxins. The authors therefore made

experiments to determine whether by the administration of cholesterin to animals (mice, guinea-pigs, rats and rabbits) feeding them for several weeks, giving 50 mg. daily to mice and 100 mg. daily to the other animals, they could change the course of experimental bacterial infections (pneumococcus, pyocyaneus, staphylococcus, anthrax) and intoxications (diphtheria toxin). They found as a matter of fact that some of the animals fed with cholesterin survived the infections and that some of them lived longer than the control animals. In noninfected animals that were examined the cholesterin content of the blood was found higher, in control animals lower. Cholesterin does not show a direct disinfectant action in plate experiments. Nor does blood with an increased cholesterin content show any bactericidal action. The latter does not, therefore, increase the phagocytic action of the leukocytes. Cholesterin seems therefore to act only by fixing toxins, which is indicated also by the authors' experiments with diphtheria toxin. Hence the course of the infection depends, on the one hand, on the amount of toxins, on the other hand, on the amount of blood cholesterin which is available for combining with the toxins, and, in the further course of the disease, on whether the cholesterin used up in this way can be satisfactorily replaced. The poverty of the suprarenals in cholesterin is a result of the hypocholesterinemia; whether it alone causes the changes in the suprarenals, or whether there is also a direct action of the toxins in infections, is not definitely known.

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**The Bacteriophage (Bacteriolysin). I. The Nature of Bacteriophage.**

*F. d'Herelle, Brit. M. J., London, p. 289, Aug. 19, 1922.*

The bacteriolysis produced under the influence of the principle named bacteriophage consists in a total dissolution of the microbial body; at the end of this action there remains no visible residue. A total dissolution of a microbial substance can only be due to a transformation or decomposition of the proteins of the microbe by proteolytic enzymes. Four hypotheses are considered concerning the source of these enzymes: (1) The enzymes may be derived from the animal organism which is attacked by the given bacteria, and would then be the result of a defensive reaction on the part of the organism. (2) They may come from intestinal bacteria as the result of a microbial antagonism. (3) They may be secreted by the bacterium itself which undergoes the lysis, and would therefore be autolysins. (4) They may be secreted by an ultramicroscopic virus, which is a parasite of bacteria, as the author believes.

Hypotheses 1, 2, and 3 are eliminated by the following experimental facts: (1) The dissolution of bacteria under the influence of the bacteriophagic principle takes place in series; (2) the lytic enzymes emanate from material corpuscles which traverse filters; these corpuscles multiply in the course of the bacteriolysis; (3) all bacteriophagic ultramicroscopic corpuscles, grown at the expense of any bacterial species, constitute one and the same antigen. Hypothesis 4 is alone admissible and is not contradicted by any of the experimental facts. The

ultramicroscopic corpuscles possess a variable virulence, and by successive passages, it is possible to increase the virulence of a feeble strain of bacteriophage: experience shows that bacteria attacked by bacteriophage do not remain passive; they defend themselves and are even capable, under certain conditions, of acquiring an immunity toward the parasite. The behavior of bacteriophage toward physical and chemical reagents is that of a living being, and does not agree with that of an enzyme as it is possible to extract the lytic enzymes free from the living bacteriophage microorganism. Bacteriophage is capable of adaptation, for its properties are essentially variable.

Furthermore, all of the facts cannot be explained if this hypothesis is abandoned or modified; therefore such a hypothesis becomes a certitude. The author does not specify the species to which the ultramicroscopic organism belongs; all that is known is that it is a filtrable being, parasite of bacteria, endowed with functions of assimilation and reproduction.

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**The Bacteriophage. II. The Breaking Down of Bacteria by Associated Filter-Passing Lysins.**

*F. W. Twort, Brit. M. J., London, p. 293, Aug. 19, 1922.*

The object of the author's research was to discover, if possible, the nature and life-history of the ultramicroscopic group of viruses; attempts were made to demonstrate the presence of nonpathogenic filter-passing viruses. First experiments were carried out with such material as soil, dung, hay, straw, and pond water; also on pathologic material obtained from distemper in dogs, from vaccinia, and other sources. The conclusion drawn is that it seems probable, though by no means certain, that the active lytic material is produced by the micrococcus, and since it leads to its own destruction and can be transmitted to fresh healthy cultures, it might almost be considered as an acute infectious disease of micrococci. Where differences of opinion exist, the controversy has centered chiefly round the experiments carried out to determine the source and nature of the lytic material.

Recent experiments have in no way changed the author's views regarding the lytic agent of the micrococcus, viz. that the possibility of its being an ultramicroscopic virus has not been definitely disproved, and that probably the active transparent material is produced by the micrococcus. He holds the same view regarding the lytic agent which he and various workers have found associated with the dysentery-typhoid-coli group of bacilli. In pure cultures of such bacilli as dysentery, typhoid, and coli, one sometimes meets forms considerably larger and longer than the average bacillus, and these may be found in pathologic material containing these bacilli, being not uncommon in urine in cystitis cases. Experiments have shown that the large bacilli proved to be special forms of the bacterium from which they were obtained, and were easily agglutinated by the specific serums: they were more pathogenic when produced by normal bacilli than after repeated multiplication by division; when isolated and grown they became more resistant to the lytic agent. The author admits that some views suggested here are doubtless open to criticism, but claims that the discovery of the filter-passing lytic agent in association with bacteria offers a



large field for research, and suggests that this field has been further extended by the isolation of special forms of bacteria, and by the possibility of demonstrating the production of bacterial antitoxins for the neutralization of toxins produced by other varieties of bacteria.

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**The Bacteriophage. III. Concerning the Theories of the So-Called "Bacteriophage."**

*J. Bordet, Brit. M. J., London, p. 296, Aug. 19, 1922.*

The author seeks to correct misinterpretation of his theory concerning the lytic phenomenon due to the so-called bacteriophage by restating the theory already published. He and his coworker Dr. Ciuca were the first to advocate the view that the lytic principle is produced by the microbe itself which shows the lysis—in other words, that the transmissible lysis is in reality an autolysis betraying a nutritive vitiation primarily started by external influences, an example of which may be the contact with a leukocytic exudate. The following passages in their papers where this assumption is advocated are submitted in proof: "External influences such as that of a leukocytic exudate modify the bacterium, inducing the latter to elaborate a lytic substance capable of diffusing itself and bringing about the same autolytic phenomenon through successive cultures. When the autolytic process occurs a large number of the microbes present may perish, but some of them, being more resistant, are, during a certain length of time, still capable of reproduction in spite of their producing the active principle, thus imparting to new cultures of the same microbe the same autolytic tendency." "According to d'Herelle, the lysis is due to a living being, to a filtering virus. We, on the contrary, believe that the lytic principle originates from the bacteria themselves, which, when touched by this active substance, are capable of regenerating it, the factor responsible for the phenomenon being thus unceasingly reproduced—on the condition, however, that the bacteria be still living and provided with the alimentary substances necessary to their growth."

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**The Bacteriophage. IV. Concerning the Theories of the So-Called "Bacteriophage."**

*André Gratia, Brit. M. J., London, p. 296, Aug. 19, 1922.*

Facts concerning some theories already advanced are presented. The opinion is expressed that the Twort and d'Herelle phenomena are identical, being two different aspects of one and the same phenomenon: the transmissible lysis of bacteria. There are no unquestionable proofs that the bacteriophage is a living organism. The assumption of the bacteriophage being a filtrable virus for bacteria was suggested by two main facts: (1) the power of reproduction possessed by the lytic agent; (2) the localization of the lysis to certain round spots of clarification when a very diluted lytic agent is poured over the surface of an agar culture of sensitive bacteria. Although easily explained by the virus theory, yet both facts are not unquestionable proofs of the

living nature of the bacteriophage, because they are by no means exclusive features of living beings. The idea of the bacteriophage being a product of bacterial activity is suggested by the close parallelism existing between the regeneration of the lytic agent on the one hand, and the activity of growth of the bacteria on the other hand. The conception of the bacteriophage being a chemical substance is favored by the chemical-like affinity existing between a given lytic agent and the corresponding susceptible strain. The bacteriophage is not one and the same antigen. Several lytic agents showing antigenic specificity must be considered.

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**The Bacteriophage. V. Concerning the Theories of the So-Called "Bacteriophage."**

*J. C. G. Ledingham, Brit. M. J., London, p. 297, Aug. 19, 1922.*

The author feels that there has been little attempt to study the phenomena on quantitative lines, in order to eliminate or evaluate the various known possible factors and agencies that may, in conjunction or separately, give rise to the end-result. However, from data recorded, certain facts are presumably established. Certain organisms, particularly those of the intestinal group, submit readily to lysis under the influence of a variety of primary stimuli. These may be filtered fecal extracts from healthy or diseased persons, or may be extracts of normal tissues or body secretions. Filtrates of these organisms so dissolved are able to carry on the process. While some strains of these same organisms are naturally resistant to these same stimuli, other strains show lytic changes normally—an important fact. The stimulus if not too strong causes a dissociation of the strain acted upon, into resistant and nonresistant types. Potent lytic extracts can be prepared from the organisms themselves during artificial growth, the process being apparently facilitated by repeated filtration of the growth and re-inoculation of the filtrate with the organism concerned. Potent lytic extracts can be obtained from the filtered growth of organisms growing symbiotically. However the initial stimulus is obtained, the transmission in series can, in the author's opinion, be explained only on the assumption that potent autolytic ferments discharged from the lysed organisms are able to initiate similar effects in passage. The author argues for the investigation by quantitative methods of the simplest form in which the phenomenon can be elicited. Two main factors are: (1) the variability of bacteria in the matter of susceptibility to lytic change; and (2) the lytic action of extremely finely divided colloidal bacterial protein on susceptible bacteria. From such interaction would result the liberation of autolytic ferments capable of repeating the process in series.

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**The Bacteriophage. VI. Concerning the Theories of the So-Called "Bacteriophage."**

*J. W. McLeod, Brit. M. J., London, p. 298, Aug. 19, 1922.*

The observations on which d'Herelle based his case for proving the existence of an invisible bacterium parasite of the species under investigation, i. e. the development of bare spaces amid the growth on an agar

slope when the latter was inoculated from a bacterial emulsion to which a small amount of bacteriolytic filtrate has been added, do not appear to the author to differ essentially from the older results of Eijkman on auto- and hetero-inhibitions in bacterial cultures. Eijkman brought out the points that most, if not all, bacteria produce in the course of their growth substances inhibitory of that growth and that in the case of some bacteria the substances produced act as powerfully, or more so, on other bacterial species; that these substances are thermolabile. From work on the subject of the production of bactericidal substances by bacteria, the writer concludes they are diverse. In thermolabile bactericidal substances produced by pneumococci and many streptococci which were thought to be of complex constitution and protein in nature, it was found that the substance responsible is hydrogen peroxid. The substances inhibiting growth produced by the coliform group of bacteria are certainly different. An attempt to determine the nature of the inhibitory substance in filtrates of *B. coli* cultures showed that it was not thermolabile, but was readily thrown out of action by dilution or by addition of alkali. Shiga's bacillus was found to be most sensitive in its growth to inhibition by many varieties of bacteria.

The author finds it impossible to accept d'Herelle's theory without more satisfactory proofs than those already advanced, since d'Herelle has claimed for his microörganism 2 characteristics which are without parallel in bacteriologic observation: (1) a heat resistance on the part of the bacteriophagum greater than that demonstrated in connection with any other ultramicroscopic virus occurring in the animal body; (2) an organism which grows actively in fluid mediums without production of turbidity.

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#### **Experiments Employing a Quantitative Method in a Study of the D'Herelle Phenomenon.**

*H. B. Maitland, Brit. J. Exper. Path., London, 3: 173, Aug., 1922.*

The phenomenon of d'Herelle consists, in general terms, of changes in bacterial cultures initiated by some substance of obscure nature that has been obtained from diverse sources. One of the striking changes is lysis, indicated by clearing of a bouillon culture. In this paper the substance is referred to by the author as the "active" substance. To determine the rate of increase of active substance in bouillon cultures, active substance, obtained from the patient, and *B. dysenteriae* were employed. To each of several identical tubes of young bouillon culture was added an amount of active substance known by previous determination to give a reading of about 300000. The tubes were placed at 37° C. From time to time one was filtered through a Mandler filter and the strength of the filtrate measured. Thus a number of readings were obtained giving the strength of samples at various times. A control of active substance in bouillon in every instance showed no increase. There was an early period of lag, a short period of rapid increase and an indefinitely prolonged period of equilibrium. The increase of the active principle did not coincide with any constant alteration in the total bacterial content of the culture in which it was increasing. Lysis did not always occur; sometimes there was increase in the total number of bacteria.

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**Bacteriophages (Phenomena of Twort and D'Herelle).**

*R. Doerr, Klin. Wchnschr., Berlin, 1: 1489, 1537, July 22, 29, 1922.*

By bacteriophagy, transmissible lysis or d'Herelle's phenomenon, is understood the fact that certain kinds of bacterial cells in the phases of active metabolism and reproduction may be quickly dissolved and destroyed by nondialyzable, thermolabile substances which pass through clay filters that are impermeable to bacteria and rapidly increase in amount during the bacteriolysis caused by them. The increase of the solvent substances is connected with the exercise of their function and the latter with the presence of soluble bacteria; the solvent substances which have an unlimited capacity for increase are true antagonists of the bacteria and represent a new factor in the struggle between the host and the bacteria. With reference to the nature of the active principle it is undecided whether it is due to an ultramicroorganism or to a catalytic enzyme. Twort first described bacteriophagy in 1915, but no attention was paid to this until d'Herelle in 1917 described the phenomenon and developed the theory of "transmissible lysis" now generally recognized. The bacteriophages are probably found in the intestinal discharges of all animals and fulfil the function of antagonistic regulators of the growth of the normal and pathologic intestinal flora; from the intestine the lysins pass into the soil and the water where, as pre-formed substances or in combination with lysinogenic bacterial cells, they retain their effectiveness. But as there are lysins against staphylococci, plague bacilli, and other microorganisms, there must be other places than the intestine where the lysins originate and increase. The most important question is the proportion of the soluble bacterium to the dissolving agent. As the lysins pass through a filter through which bacteria cannot pass, and as they are resistant to an hour's heating at 57° to 60° as well as to chemical disinfectants, germ-free filtration and inactivation offer methods of separating the lysins from the bacteria. It is impossible to get solutions of lysin that are free from products of bacterial disintegration nor does dialysis offer means of separating them. The lysins only pass through membranes when the latter are permeable to native horse albumin; therefore they consist of molecules of the size of antigen colloids. Studies by the author of the relations between increase of lysin and propagation of the bacteria showed that the latter is an essential condition; during latency of growth, living microbes and lysin do not have any effect on each other in an optimum nutritive fluid. Propagation of bacteria precedes a rise in bacteriophage titer; the death of the bacteria first overcompensates their reproduction when the bacteriophage titer has reached its maximum; in the last phase of the greatest destruction of bacteria there is no essential increase in the bacteriophage titer; the increase in amount of the lytic substances is rapid, but absolutely continuous. As the living, resting bacterial cells are not injured by the lysin, but only the growing and dividing cells, the author ascribed to the carrier of the bacteriophagic action the character of a metabolism toxin that is secreted by the diseased bacteria, for which there are analogies in pathology. The injury of the bacterial cells by the lysins need not proceed to solution, but may become manifest as dysfunction. By the addition of gelatin it is possible to demonstrate defective gas formation, abundant coarsely flocculated agglutination and

changed intensity of growth in the culture; a slight addition of gelatin even acts as a stimulus of growth. Bacteria grown in a medium that contains lysins show morphologic variations that may be regarded as pathologic. More important functional variations occur in bacteria that survive the effect of the lysins; such bacteria may produce the lytic substances when they propagate, but they and their descendants may become resistant to them. The capacity for producing lysins and resistance to lysins is not always associated. Another pathologic characteristic of resistant and lysinogenic cultures is that they are no longer influenced by the bacterial antibodies. The acquired capacity for lysinogenesis is limited to one strain of bacteria, but from a lysinogenic strain other bacteria can be propagated that do not produce lysins and have a pronounced sensitiveness to them, while by the ordinary methods, lysinogenic, resistant and normal bacteria can be separated. The bacteria may also be cured by serotherapy. The lysogenic bacteria become normal again when cultivated in a medium containing antilysins made by adding antilytic immune serum to the medium. In distinction from bacterial protein antigens the lysins have no specificity, but there is individual specificity between lysins and antilysins in different strains. Unlike the bacteria the lysins are polyvalent as well as monovalent, most frequently the former in lysins of the typhoid-colon group. As the antilysins in conjunction with their antigens fix complement they have an amboceptor character. The lysins belong to the protein antigens, and as their combination with the amboceptor destroys their biologic function, there may be a connection between their antigenic power and their capacity for injuring bacteria.

Bouillon which contains lysin and samples of feces containing lysin maintain their activity for years at room temperature; evaporated bouillon containing lysin, when dissolved in water, shows activity again after months. Lysins are fairly sensitive to free H and OH ions. The reports on the heat resistance of bouillons containing lysins vary greatly, 56-64° C. weakens the lysins even after a short time, 65-75° C. destroys them entirely. The striking sensitiveness of lysins to neutral quinin solutions is cited as evidence of their microbic character. In addition to the factors which destroy lysins there are others which only inhibit or prevent the occurrence of d'Herelle's phenomenon (bacteriolysis) but leave the lytic principle intact, so that after the removal of the disturbing factor the latter regains its characteristic action and manifests its capacity for increase. Among the "lysin antagonists" are sodium fluorid, chloroform and calcium chlorid in subthreshold concentrations and with a short period of action, while in stronger concentrations and with more prolonged action they destroy the lysins completely, as do also high oxygen concentrations. Lysis occurs between 0° and 42° C., most rapidly between 37° and 40°. D'Herelle's theory that the causative agent of the action is a pathogenic ultramicroörganism is rejected by the author as unfounded, as the experiments in support of this theory can also be interpreted as lending support to that of an inanimate, colloidal soluble substance which is toxic only for bacteria. An argument against d'Herelle's theory is the great resistance to chemical disinfectants with slight resistance to heat. Nor can the existence of "tâches vierges," which have been regarded as colonies of bacteriophages, be used as an argument for d'Herelle's theory; they are the natural results of the fact that lysins in contact with growing bacteria also increase in



amount, and have nothing to do with the size of the lysin particles dispersed in aqueous fluids. The solubility of lysins corresponds to that of a high-molecular albumin colloid. In explaining the "tâches vièrges" not only the active substance but also the bacteria must be taken into consideration. The presence of lysinogenic bacteria is sufficient to transmit the disturbance to the normal bacterial population. D'Herelle's theory presupposes that bacteriophagy must always be brought about by the deliberate addition or the primary presence of the ultramicroörganisms, while the theory of a metabolic disturbance of the bacteria makes this assumption superfluous. The assertion that the leukocytes play a part in the changes in the bacteria has not been generally confirmed. It has been shown, however, that the lytic agent can be obtained from cultures of apparently normal bacteria without the action of a higher organism. The primary point of origin of the lysins is in the bacteria. There is nothing to show that very small bacterial albumin molecules endowed with fermentative characteristics are formed on the breaking down of the living cell. Nor has the fermentative character of the lysins been proved. D'Herelle's phenomenon cannot therefore be compared with autolysis, as the former only affects growing bacteria and ends with the destruction of the bacteria, while by autolysis living and dead cells are broken down into simple split products. The author could not confirm the assertion that there is progressive decomposition of the bacteria after lysis. He agrees with Bordet that an inheritable disturbance of metabolism of the bacteria is the chief factor and that the lysins are growth hormones which under certain conditions are given off from certain bacteria.

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**Experimental Study of the Relations of Bacteria and Bacteriophages (Transmissible Lysins) to Bile.**

*R. Doerr and W. Grüniger, Schweiz. med. Wchnschr., Basel, 52:761, Aug. 3, 1922.*

Following up the experiments of Kabeshina, the authors studied in animal experiments the action of colilysin on a strain of colon bacilli closely related to typhoid bacilli. In preliminary experiments they studied the passage of lysins from the circulation of rabbits into the gall-bladder and the length of time they remained in the gall-bladder. (1) Colilysins injected intravenously into rabbits were excreted with the bile or urine, but they could be demonstrated only shortly after the injection and in small amounts. (2) The greater the amount of lysin injected and the stronger its concentration, the greater was the lytic action of the urine or bile. (3) The passage of lysins into the bile is more rapid and greater in small animals. (4) Within 14 hours after the lysin injection, that is almost at the time of the fall of the lysin titer in the circulating blood, lysin can no longer be demonstrated in rabbit's bile. Rabbits or guinea-pigs cannot be transformed into carriers of bacteriophages. Attempts were made to introduce lysins prophylactically or simultaneously with the bacteria upon which they act. After intravenous injection of a certain quantity of bacilli permanent carriers were much rarer than when they were injected at the same time with the proper transmissible lysin, and such simultaneous injection

produced lysinogenic and lysin-resistant strains of bacteria. Finally in a further series of experiments colon bacilli were introduced directly into the gall-bladder of rabbits and then varying doses of colilysin were injected intravenously after different intervals of time. It was found that a single intravenous injection of considerable amounts of bacteriophages did not bring about sterilization, and that larger doses caused a transformation into resistant lysinogenic strains. The negative result of this experimental attempt at sterilization is the more discouraging as it is to be feared that in man the amounts of lysin necessary to bring about the required maximum concentration in the blood are above the limits of tolerance or toxicity; moreover from the stools of typhoid bacillus carriers resistant strains could frequently be cultivated. But it is possible that repeated lysin injections may have a better sterilizing effect than a single injection.

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#### **The Phenomenon of D'Herelle.**

*R. Otto, H. Munter and W. F. Winkler, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96: 118, May 24, 1922.*

From the watery stools of dysentery patients d'Herelle obtained filtrates having an inhibitory and bacteriolytic action on the bacteria; this bactericidal action increased if the feces were kept 24 hours at 37° C. before filtering. He assumed that the culture tube contained a pure culture of bacteriophages. The size of the "Bacteriophagum intestinale" is below that of the protein molecule. The virus was obtained from the stool and incubation, from the peritoneal exudate and from cultures of typhoid, paratyphoid B, Y, Flexner, Shiga-Kruse and colon bacilli. The virus is supposed to cause a new form of interference with bacterial growth. This consists not in a complete absence of growth on an agar plate, but only in a characteristic diminution (hazy bacterial turf in paratyphoid B and staphylococci cultures). The varied (specific or polyvalent) activity of the lysins is shown by several examples. The demonstration of lysins is possible at various temperatures, but only with living bacteria. In healthy as well as nondysenteric patients dysentery bacteriophages were found. While bacteriophages were obtained from the most varied bacterial cultures (bouillon cultures) in vitro, this is easiest with dysentery and typhoid bacilli. Filtration through a bacterial filter is the important step in obtaining the lysins.

It was determined that the bacteriophagic virus is formed by the bacteria and is a ferment bound to minute parts of the bacteria, but is not a separate microörganism.

Lysin formation is favored also by addition of (a) immune serum, (b) bacterial autolysate, (c) inactivated bacteriophages, and (d) weak corrosive sublimate. Hence various measures which injure living bacteria favor lysin formation. As a rule the bacteriophagus is specific. Flexner and Y bacilli lysins act equally on Flexner and Y bacilli cultures, Shiga lysins act on Shiga and typhoid bacilli, while typhoid lysins act on typhoid and Shiga bacilli. Mutation of the virus to act on different bacilli is not always successful. The virus is potent for considerable time, when preserved at 8°, 22° and 37° C. Some cultures spontaneously become resistant to the virus.

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**D'Herelle's Phenomenon.**

*C. Prausnitz, Klin. Wchnschr., Berlin, 1:1639, Aug., 12, 1922.*

The author examined bacteriophages to determine whether they are an ultravisible living virus other than bacterial, or whether they represent a dead ferment derived from bacilli. To determine the effect of the various filtrates, he employed d'Herelle's method of counting the bacteriophage colonies. By filtration through Berkefeld filters only a small amount of filtrate was lost by adsorption, and the filtrate lost its properties only after repeated filtration. Bacteriophages have marked dispersibility and are large enough to be measured, like collargol (perhaps 20 mm.), whereas pepsin, trypsin and invertase are much smaller and can pass through the finest filtering membrane. Certain chemicals of the naphthalin series, especially tetralin, destroy bacteriophages, but have no effect on the aforesaid ferments.

If a bacteriophage were a part of a bacterium, such as a ferment or a bacterial derivative, it would, after having been saturated with the antibacteriophagic serum of that bacterium, lose not only its antibacterial but also its antibacteriophagic properties. That this is not the case is sufficient proof that bacteriophages are not derivatives of bacilli but are in their chemical structure entirely different from the latter. The fact that antibacteriophagic serum still retains its properties after having been heated to 75° C. justifies the assumption that the serum contains specific heat-resisting antibodies against the bacteriophages, and that these antibodies are perhaps complemented by a nonspecific ferment contained within the body of the bacteria. By neutralizing a bacteriophage with an antiserum the author was able to cultivate a bacteriophagic strain which was almost serum-fast. These facts confirm d'Herelle's claims that bacteriophages are an ultravisible virus.

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**Ether Sensibility of Antibodies.**

*J. Forssmann, Biochem. Ztschr., Berlin, 130:154, June 20, 1922.*

Former experiments have shown that, when the Wassermann substance is precipitated together with the globulins from positive serums and the precipitate is dissolved in a salt or a soda solution, the Wassermann substance thus dissolved is not altered either by treatment with ether or by inactivation, but that the solution retains its former Wassermann reaction while it is destroyed or rendered inactive by ether treatment and subsequent inactivation. This circumstance was utilized to furnish proof of the probable antibody nature of the Wassermann substance. Normal antibodies as well as those produced by immunization were employed for this purpose.

The experiments gave the following results: The Wassermann substance, precipitated from positive serums and dissolved in a salt or a soda solution, is destroyed by treatment with ether and subsequent inactivation. The normal sheep hemolysins of human serums, whether occurring in the serums or dissolved in a salt or a soda solution after precipitation from these serums, show exactly the same behavior toward the same treatment as the Wassermann substance. This applies also to the immune sheep hemolysins of rabbit's serum provided they are

dissolved in a salt or a soda solution. Agglutinins, namely normal agglutinins against guinea-pig's blood-corpuscles in ox serum, as also typhoid-immune agglutinins of rabbit's serum, do not react at all or barely perceptibly to the aforementioned ether treatment. This ether reaction is to be regarded as an adsorptive, and not as a stereochemic, reaction. As different antibodies (hemolysins and agglutinins) show different behavior toward the reaction, they do not furnish a proof of the nature of the Wassermann substance, that is, whether it represents an antibody or not.

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**Serologic Experiments with Antigens and Antibodies on the Excised Perfused Liver. III. Experiments with Agglutinins.**

*M. Hahn and E. von Skramlik, Biochem. Ztschr., Berlin, 130:80, June 20, 1922.*

While it is possible to throw light on the process of agglutination in vitro and partly also intra vitam the behavior of agglutinins toward body cells is obscure. It is known that the organism endeavors to relieve itself of agglutinins to a certain extent, as is shown by the occurrence of agglutinins in the urine. However, the conditions are by no means so simple as might be assumed from this fact, because agglutinins remain in the circulation a long time even when the microorganisms responsible for their occurrence have long ceased to be detectable. It might be assumed either that agglutinins are formed permanently or that during the infectious process agglutinin reservoirs are established in the body from which agglutinins are supplied continuously to the blood. Experiments were undertaken to clear up this question. Artificial perfusion of the liver proved a suitable method. Typhoid and colon bacilli agglutinins in 1:1000 dilution were studied in the artificial circulation through the guinea-pig liver. It was found that circulating agglutinins are taken up by liver tissue in small amounts during a prolonged experimental period and they cannot be removed by mechanical means. A quantitative difference exists between the retained amounts of typhoid and colon bacilli agglutinins, the former being retained in much larger amounts. In the experimental procedure the agglutinins are poisonous to organic cells. Considerable amounts of protein occur continuously in the circulating fluid. If a suspension of suitable bacilli is passed through an organ that was perfused an hour with agglutinin and then washed out completely with Ringer's solution, agglutination takes place in the capillaries. The number of bacilli is diminished in the course of a few minutes to 10-5%. Proof of agglutination was furnished by histologic examination of the organs.

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**The Relation between the Accumulation of Globulins and the Appearance of Agglutinins in the Blood of New-Born Calves.**

*Marion L. Orcutt and Paul E. Howe, J. Exper. Med., 36:291, Sept. 1, 1922.*

The authors discuss the relation which exists between the appearance of agglutinins for *Bacillus abortus* and the accumulation of

globulins in the blood of new-born calves, and upon the protein fractions in the colostrum and blood with which the agglutinins are associated.

The method of collecting samples of blood, and the determination of the agglutinin titer of blood and colostrum have been presented in previous papers. The procedure for the determination of the proteins of blood and colostrum has also been given. Samples of colostrum and of serum with high agglutinin titers for *Bacillus abortus* were fractionated with sodium sulphate at 37° C. to determine the protein fraction or fractions which would contain the agglutinins. Proteins when precipitated are readily soluble in water and salt. The general procedure for separation of protein fractions was to precipitate small quantities, 0.5-1.0 c.c. of colostrum or serum, with various concentrations of sodium sulphate, wash the precipitate with the concentration of sodium sulphate used in the precipitation, and then to dissolve the precipitated protein in a known quantity of distilled water. The final concentration of the protein was then known within approximate limits. The procedure for testing the associated agglutinins has been described elsewhere. That the salt in itself did not cause agglutination nor inhibit agglutination at high dilutions was demonstrated by control experiments.

The data presented with regard to the precipitation of agglutinins for *Bacillus abortus* in blood and colostrum indicate definitely that the protein, or protein mixtures, precipitated up to and including 16.4% of sodium sulphate, carry with them the agglutinins. It is this fraction, which is absent from the blood of the new-born calf, which is abundant in most samples of colostrum and which is absorbed directly by the new-born animal. Neither the association of immune bodies with globulins nor the direct absorption of protein by new-born animals is a new fact. The evidence presented is of particular value, however, in associating the appearance of certain protein fractions in the blood of the new-born animal with the simultaneous absorption of agglutinins.

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**Spontaneous Agglutination of Bacteria in Relation to Variability and to the Action of Equilibrated Solutions of Electrolytes.**

*Ralph R. Mellon, J. Med. Research, 43: 345, June-July, 1922.*

In 1901 Bordet made the important generalization that the phenomenon of flocculation is due directly to the pressure of electrolytes; it was not known, however, whether this action was caused by sodium chlorid in its molecular form or whether it was due to the anions or the cations. Later, Jacques Loeb proved rather conclusively that, for the eggs of *Fundulus*, the toxic action is attributable to the cation. He also showed that there is an antagonism between such cations as sodium, potassium and calcium and that the protective action of such balanced or equilibrated solutions as Ringer's and Tyrode's owe their equilibrium to the mutually antagonistic actions of the cations. This principle of ion antagonism suggested an applicability to the phenomenon of bacterial agglutination.

The organism chosen was a diphtheroid showing extreme agglutinability, which had been isolated as a contaminant on a blood-agar plate. The solution of the problem depended on the observation that the culture



had two morphologic phases of growth: a bacillary phase requiring a temperature of 37° C., and a diplococcus phase requiring a temperature of 20° C. Of 7 single cells planted, 5 were viable. Four of these remained true to type in that incubation at 37° C. produced agglutinable bacilli while growths at 20° C. resulted in easily emulsified cocci. Transplants subjected to the reverse condition assumed the reverse form. The fifth culture produced a mutant, a strain which did not show the reversibility just described but which produced agglutinable bacilli when grown at 20° C.

The suggestion that pleomorphic forms represent a phase of the organism which resists the toxic effect of environment correlates well with the readiness of these forms to emulsify in sodium chlorid and also indicates that they are probably not susceptible to the sodium ion.

Some of the 37° C. cultures gradually became emulsified after standing at room temperature for some time. Certain of these were emulsified by equilibrated solutions while still agglutinable by sodium chlorid. Not all equilibrated solutions, however, had the same effect even on the same culture. A progressive stabilization of the organisms was observed, one extreme being represented by immediate and complete precipitation in sodium chlorid, an intermediate stage being characterized by partial precipitation in Ringer's and Locke's solutions, and the other extreme by perfect emulsion in Tyrode's solutions. This phenomenon seemed to be associated with secondary growth changes in the culture, consisting of secondary or daughter colonies which were regarded as the macroscopic counterpart of the pleomorphic forms. Besides throwing light on the nature of secondary colonies, evidence is furnished for the theory of morphologic bacterial growth cycles with physiologic connotations. Spontaneous agglutinability is thus seen as a function of bacterial variability.

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**Preventive Vaccination in Man by the Digestive Tract against Bacillary Dysentery and Mediterranean (Malta) Fever.**

*Charles Nicolle and E. Conseil, Ann. de l'Inst. Pasteur, Paris, 36: 579, Aug., 1922.*

In order to be conclusive for man, vaccination tests must be made in human subjects. Such tests are permissible with infections not naturally dangerous, or for which sure therapeutic cure is available, as in bacillary dysentery and Malta fever. These conditions are especially useful for tests, since the effects of the former are mainly local, those of the latter principally general. Preventive subcutaneous vaccination against Malta fever may be readily obtained by injecting killed cultures. The authors' cultures were grown for 24 hours on agar, centrifugated, washed and mixed with 7 to 1000 NaF solution, incubated for 4 days at 37°, for 2 days at 50° and proved sterile. Mixtures from several cultures were made. The injections consisted each of 1 c.c., containing 900 millions *M. melitensis*. The immunity acquired lasts less than 5 months, so that repeated injections are necessary. For test by mouth, cultures were prepared as before, except that they were not washed, and were sterilized by heating for 1 hour at 72° to 75°. Vaccination by mouth proves as satisfactory as when made subcutaneously. The immunity thus acquired is equally brief. In the subcutaneous tests,

1800 million bacteria were given, in 2 injections. In the tests by mouth, a total of 400,000 millions were given, in 4 doses. In 1916, intramuscular vaccination tests were begun among troops located at Tunis. Some 1018 individuals were vaccinated, but military exigencies prevented completion of the tests. The first dose did not exceed 250 millions, the second, made in about 2 weeks, ranged from 250 to 750 millions. It was found that edema produced during an incubation period following injection could be greatly ameliorated by an injection of 2 c.c. anti-dysenteric serum.

The reaction following intravenous injection of living or dead bacilli of Shiga is too severe to render this method practicable. Moreover, even toxic doses (450 millions) do not produce conditions resembling the disease as occurring naturally. In testing vaccination by mouth against Shiga's bacillus, the adverse conditions consisted of the delicacy of the virulence of these organisms when cultivated, and a marked resistance to the infection among natives of Tunis where the tests were made. Experiments by mouth and rectum showed that the conditions essential for reproducing dysentery experimentally by the human digestive tract depend on individual susceptibility, which varies with different races, and on having an active culture, secured by employing a recently isolated virulent strain of bacilli. Vaccination tested by mouth in Europeans proved effective.

Vaccination by mouth against Malta fever and dysentery is entirely satisfactory. The minimum dosage should be determined and the duration of immunity ascertained. The method will probably prove equally applicable to infections usually entering, and causing local lesions of, the digestive tract, such as typhoid, paratyphoid and cholera.

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### **The Rôle of Tropins and Antitoxins in Experimental Cholera Immunity.**

*Otto Ornstein, Ztschr. f. Hyg. u. Infektionskr., Berlin, 99:70, May 24, 1922.*

In various experiments all fresh cholera strains proved to be hemolytic. But in cultures they usually lose this property rapidly; only few show this quality in high degree and in these it can be preserved by appropriate passages. Studies were made on the rôle of the various immunity functions in cholera by testing serums prepared with variously treated antigens.

It was sought to answer the following questions: Can the antigenic effected be divided by separating the soluble toxins from the vibrio? What changes in the antigenic effect result from autolysis of the vibrio at 37° C. or from heating the toxin at 60° C. for an hour? Can precipitation with an agglutinating or bacteriolytic serum (with only traces of tropin and antitoxin activity) achieve separation into bacteriolysinogen and antitoxinogen? How is the feeding immunity manifested serologically?

From the serologic investigations it may be concluded that the immune serums which have little or no bactericidal activity in the test-tube, have the specific property of causing a very powerful phagocytosis both in the test-tube and in the body, which is due to the presence of a

bacterioscopic substance in serums. That the bacteriolytic function is a temporary early phase of immunity may logically be concluded from the earlier appearance of lysins than tropins and especially from the greater prophylactic value of tropic-antitoxic serum. In feeding experiments, young rabbits (600-800 gm.) invariably die in a few hours after a comparatively small quantity of virulent, toxin-forming vibrios (suspension of about one-fourth of an oblique culture) with signs of acute poisoning and general infection. Small quantities (loopful) of a living culture killed experimental animals in 4-23 days. The vibrios could be demonstrated in pure cultures in the small intestine and cecum (in 4-14 days), but only rarely in the blood shortly after death of an animal. Atoxic vibrios do not have this action. Hence the toxin of cholera vibrios plays an important rôle in infection, and the disease in human beings is doubtless a poisoning.

The experiments indicate that the antigens found regularly in fresh and highly virulent cultures are very important in immunization against cholera. These antigens may be absent in older and less virulent cultures and are destroyed by heat of 56°-60° C. and prolonged autolysis at 37°. They are characterized by strong hemolytic activity in vitro and by very toxic activity in experimental animals. As these antigens are largely responsible for the formation of antitoxins and bacteriotropins they should be given consideration in prophylactic vaccination. For vaccines highly virulent (preferably fresh) cultures with strong hemolytic power should be used, and these should be killed with great care (phenol is best) and should be protected from high temperatures. The dosage of such a vaccine should be determined by experiment. For further study of serum prophylaxis and therapy in cholera, the serum should be prepared from potent poisons of toxic, highly hemolytic strains.

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**The Pathogenesis of Cholera. The "Intestinal Cholera" of Young Dogs.**

*G. Sanarelli, Ann. d'igiene, Rome, 32: 349, May, 1922.*

In this sixth memoir on the subject the author describes further experiments on the pathogenesis of cholera carried out on new-born dogs, from which he believes it possible to draw certain general conclusions: The dogs as soon as they are born, before they have commenced to take the maternal milk, are more sensitive to cholera infection given by the mouth. The vibrios administered by mouth to new-born dogs cannot traverse alive the normal gastric contents whose degree of acidity is very high. But, as in new-born rabbits, the vibrios are absorbed from the buccopharyngeal mucosa. Penetrating into the general circulation they soon arrive at their natural excretory site, that is in the digestive apparatus. The vibrios multiplying in the blood are soon excreted by the intestine. The multiplication of the vibrios that have penetrated into the blood and various organs is also facilitated by the absence of the bactericidal power, which does not appear in the blood serum of young dogs until 3 or 4 days after birth. The blood serum of adult dogs, on the contrary, is markedly vibriocidal. The intestinal secretions of dogs are not a favorable nutritive medium for the development of the vibrios. The absorbing power of the intestinal mucosa

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in the normal state for the vibronic proteid is, in dogs, insignificant. Only when, following vaccination by the parenteral route, the blood serum has gained a high degree of agglutinating power, does this appear in a measure, even in the intestinal mucosa. The gastro-intestinal excretion of the vibrios is shown, in new-born dogs, even if the microbes have been injected submucously or intravenously.

The reaction caused by the vibrios on the gastro-intestinal apparatus is analagous to that already observed in guinea-pigs. It consists of a gastro-enteritis with a disappearance of acidity from the gastric secretion. This secretion becomes, therefore, alkaline, and permits the growth of the vibrios and other microbes. The infection by cholera vibrios in new-born dogs, whether it has been provoked by the oral, subcutaneous, or intravenous route, always renders the colibacillus virulent. This microbe installs itself very early in the oral cavity of the new-born, probably in consequence of maternal contamination, and soon migrates toward the intestinal walls. The virulent action of the colibacillus is accompanied by a prodigious multiplication of these organisms along the entire digestive tract and is followed by their diffusion in the blood and in the different organs. As happens in human cholera, other kinds of bacilli may become virulent along with the colibacillus and may irrupt into the circulation.

Only 24 hours after birth the vibrio infection by the oral route becomes more difficult. This is not to be attributed to the hypothetic intervention of the bactericidal power, which does not appear in the blood until later, but to the probable vibriocidal action of the maternal milk. This, being taken by the new-born dog almost continuously, exerts against the vibrios in the buccopharyngeal cavity a destructive and defensive action manifestly efficacious. When 36 hours have elapsed after birth it has not been, in fact, any longer possible to provoke cholera infection in the dogs by the oral route. This explains the inconstant and contradictory results obtained by various authors who have undertaken similar investigations.

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**The Relation of Natural Diphtheria Antitoxin in the Blood of Man to Previous Infection with Diphtheria Bacilli.**

*S. F. Dudley, Brit. J. Exper. Path., London, 3:204, Aug., 1922.*

The author's observations were made on 950 school boys who ranged in age from 11-16 years. The first series of Schick reactions were performed on 831 boys who could be divided into 2 groups: (1) "new boys" who had not come in contact with the (2) "old boys" already in the school. It was found that the boys of Group 1 were three times as susceptible as those in Group 2. The author observed that the boys of the latter group became immune during outbreaks of diphtheria and between outbreaks no immunity was developed. In the course of 3 months 32% of the susceptible boys became immune. In the course of 9 months 92% of the boys who developed clinical diphtheria became immune. The period of carrying diphtheria bacilli was always short and the author estimates that during 7 months 30% of the boys were recognizable carriers. Under such circumstances it is probable that all the boys in the school had the opportunity of being affected by the diphtheria bacillus to a slight, unrecognizable degree.

(1e—200)

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**The Formation of Bacterial Toxins. II. Diphtheria Toxins.**

*L. E. Walbum, Biochem. Ztschr., Berlin, 130:25, June 20, 1922.*

The continuous production of large quantities of strong diphtheria toxin was formerly attended by great difficulties. The cultures prepared at different times and in different bouillons yielded varying results, even to a point that some were frequently very toxic while others were quite nontoxic. The view that toxin formation is related to certain seasons proved untenable. Variations in toxin formation were also ascribed to different strains, while culture methods were described for obtaining specially large quantities of toxin. Experiments were undertaken to determine the significance of the more important factors influencing the formation of diphtheria toxin. It was found that H-ion concentration of the medium, the culture temperature and culture period, the concentration of the meat extractives, peptone, salt and sterilization play a rôle, and that optimum adjustment of these permits toxin production to be directed into definite channels. In the investigations on the importance of the bouillon's initial pH it was shown that a reaction of less than about pH 6.5 and greater than about pH 8.0 is generally unfavorable while toxin formation is almost uniform at pH 6.8-7.7, and pH 7.2-7.3 may be regarded as the optimum. The temperature optimum formation lies at 36° C., the same as the optimum for membrane formation. Attempts to obviate the great changes in pH during growth by means of phosphate and glyocoll failed. The most suitable medium for the preparation of diphtheria toxin proved to be veal bouillon with peptone. Preliminary fermentation by *Bacillus coli* culture apparently has a good effect if fermentation occurs at not too high temperature (about 20 hours at 20-26° C.); to the bouillon are added 1.5% Witte's peptone, 0.2% invert sugar or glucose and 0.5% sodium chlorid. Sterilization in autoclaves is carried out previous to the alkalization of the bouillon at its normal pH (about pH 6.2) and pH is adjusted only by addition of sterile calcined soda. The most suitable peptone concentration was 1% or higher, that of sodium chlorid 2%. The temperature to which the bouillon is raised, the duration of heating and H-ion concentration have an influence on the nutrient medium's applicability to the formation of toxin. Addition of minimal amounts of manganese chlorid (0.01 molar solution of  $MnCl_2$ ) to the medium is capable of promoting diphtheria toxin formation. Even with optimum pH toxin production decreases at 37° C. The toxin elaboration decreases rapidly with increasing alkalinity. Therefore the amounts of toxin found in a diphtheria culture are only a part, and often a small part, of the toxins formed during the entire period of growth. In the preparation of the toxins all growth-promoting factors must be augmented, while those destructive to toxin should be arrested, as much as possible. Among injurious factors the substances derived from the glass may also be of moment. Experiments on the effect of various metallic salts on the formation of lysin and toxin showed that minute amounts of these substances may often exert a considerable inhibitory or stimulating influence on the course of toxin formation. Possibly, fluctuations in the toxin concentration of the different flasks are attributable to small amounts of metallic combinations derived from the autoclave or from the glass vessels. The processes in the produced diphtheria toxin cannot be completely controlled at present.



(1e—201)

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**The Use of Fresh Unchanged Toxin in the Manufacture and Testing of Diphtheria Antitoxin.**

*A. von Wassermann and M. Ficker, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:1, May 24, 1922.*

Bingel claims to have obtained in diphtheria similar curative results with horse serum as with antitoxin. Hence, in animal and clinical experiments with a serum made from a fresh toxin of diphtheria bacilli, the results were compared with serum prepared in the usual way and commonly found on the market. Toxins were obtained from various diphtheria strains freshly derived from patients. The cultures were incubated only 20-24 hours in order to obtain the products of the younger generations of bacteria. As diphtheria in its toxic forms is an acute infection, it may be expected that in the first 24 hours the most toxins are formed free of products of decomposition. It developed that even the youngest generations of diphtheria bacilli at the height of their vitality produce no other toxin than that now used for the production of antitoxin, and that the current preparation of antitoxin as well as antitoxin determination as introduced by Ehrlich meets the most rigid requirements. There is no proof that in acute diphtheria there are produced any toxins which differ from those in the culture tube or from the usual older cultures used in manufacture of antitoxin.

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(1e—202)

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**The Effect of the Light Bath on Diphtheria Toxin.**

*Carl Sonne, Acta med. scandin., Stockholm, 56:619, No. 6, 1922.*

The author has examined the effect of the light bath on diphtheria toxin circulating in the blood of inoculated guinea-pigs. Toxins are rendered less active or are destroyed by heat. Light rays may heat the subcutaneous blood to 47° or 48° C., the effect on the blood exposed naturally lasting only a short time. However, all the blood is finally exposed to this temperature. An exposure of 2 hours to the light bath is practically equivalent to exposing all the blood for 15 minutes. A bodily temperature of 40° C. must continue for several days in order to accomplish as much toxin destruction as that produced by a 2-hour exposure to the light bath. Diphtheria toxin is considerably destroyed by heating for 15 minutes at 48° C. Injected toxin remains but a short time in the blood, being fixed by the tissues, especially those of the nervous system. The author employed subcutaneous injections because of longer duration of the toxin in the blood and also because in 1 test, light rays produced no effect on toxin injected intravenously.

The light was derived from a 50-ampère arc lamp. Ultra-red and ultraviolet rays were filtered out through a Finsen water-lens. The ray temperature was 30° C., the room temperature about 20°; 38 guinea-pigs were used in the tests, their weight being as close as possible to 250 gm. each. Injections were made, in the abdominal subcutaneous tissue, of a minimum lethal dose of diphtheria toxin. Nineteen white animals, whose backs had been depilated, were exposed for 2 hours to the light bath immediately after injection, the other 19 animals serving as controls. The animals' temperature was taken before injection and after exposure to the light. During the light treatment, it should

not much exceed the normal temperature ( $39^{\circ}$ ), otherwise the animals may exhibit excitement followed by apathy, low temperature and collapse. Regulation of the heating effect of the exposure is difficult, on account of differences in susceptibility. Various conditions required the exclusion of some of the animals from the record, leaving 13 test and 13 check animals on which to base conclusions. The treated animals clearly resisted the toxin more effectively than did the controls. The shortest survival time of the controls was 2.5 days, of the treated animals 4 days; 1 control and 5 test animals did not succumb at all. The longest survival time of succumbing controls was 5.5, of succumbing treated animals, 10 days. It is difficult to estimate the degree of resistance in the treated animals, and but reasonable to consider that the light did not produce uniform effects in all the animals. The average survival time cannot be stated. If the results be interpreted according to Arrhenius and Madsen's method, 40% of the toxin was destroyed by the light treatment. In view of the exclusion of 5 animals, required by the Arrhenius and Madsen interpretation, more than 40% of the toxin was probably destroyed.

The results of the tests are probably due to heating of the blood. Chemical light effects may be practically excluded. Application of the light treatment during the febrile period of infectious diseases would probably be dangerous, since it would raise the temperature still higher. It might be applicable during apyrexia, as in the incubation period. Its value in acute infections is doubtful. It might prove useful in chronic infections characterized by the continuous production of a thermolabile toxin. The beneficial effects of light on surgical tuberculosis cannot be thus explained, since tuberculosis does not produce a thermolabile toxin. The tests do not show how light affects tuberculosis but suggest a part of its mechanism.

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(1e—203)

**Immunization against Mouse Typhoid through Feeding.**

*Otto Ornstein, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:48, May 24, 1922.*

From former experiments it may be concluded that guinea-pigs and mice can be immunized against virulent strains of paratyphoid, if enough consideration is given to the extraordinary variations in the virulence of strains. The strains of mouse typhoid are more pathogenic for mice and guinea-pigs than are ordinary paratyphoid strains. The bacilli of hog plague are under certain circumstances still more virulent. There are close connections between the various members of the paratyphoid group so far as immunization is concerned. This is proved by parenteral immunization and by immunization acquired through food. A series of experiments were carried out on mice to attempt artificial infection by feeding with mouse typhoid bacilli, and immunization of mice against feeding of mouse typhoid bacilli. Immunization against mouse typhoid was also attempted on guinea-pigs.

Active immunization of small experimental animals against virulent paratyphoid bacteria that cause septicemia proved very difficult. The degree of immunization depends upon the development of a subchronic infection. Dependent upon the virulence of the strains an acute infection can, with more or less difficulty, be changed into a chronic infection,

which leads to a condition similar to natural immunity. The treatment of mice with dead cultures or bacilli of low virulence confers no immunity against infection. The infection in inoculated animals assumes a mild course, which to a certain degree completes the immunity, as no infection results in later feedings. The guinea-pig which is less susceptible but can be infected by feeding with highly virulent bacilli, undergoes a natural immunization process against the specific infection after even comparatively small doses (one-one hundredth of an oblique culture), corresponding to a mild case of typhoid, and conferring a high degree of immunity. Against highly virulent bacteria this immunity is not absolute. It is interesting to note, that if the animal survives for any length of time, there is a tendency for the virus to produce the same anatomic lesions as in feeding infection, with the picture of typhoid in the stage of swelling of the lymphatic apparatus. In subcutaneous and intraperitoneal injections the same lymphatic localization can be noticed (intestines, lymphatics of the mesentery, spleen). Relatively high immunity is noted only after recovery from the actual disease.

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**The Effect of the Light Bath on Typhoid Agglutinin in Human Blood and on Rabbits Injected with Killed Typhoid Bacilli.**

*Thorvald Hansen, Acta med. scandinav., Stockholm, 56:629, No. 6, 1922.*

In examining the effect of light on antibodies, the author selected typhoid agglutinin because the latter may be readily tested and measured. Its daily variation in the blood follows a definite course. The curve has 4 phases, namely absence of agglutinin for 3 to 6 days following injection; increasing agglutinin, the maximum occurring in 7-13 days; rapid decline, and slow decline, or no further change. Twenty-three patients slightly affected with lupus or surgical tuberculosis, and receiving each an injection of 1 c.c. typhoid vaccine, constituted the human test material. Of these, 11 received light baths daily, beginning 2-5 days after the injection, 2 were treated every other day, beginning 5 days after injection, and 2 daily, beginning 20 days after injection. In all these cases, the exposure lasted 2½ hours. Seven patients, beginning 12 to 15 days after injection, and 1 patient, beginning 7 days after injection, received an initial exposure of 45 minutes, gradually increasing to 2½ hours. Arc lamps of 75 ampères and 50-55 volts were employed. Eight patients were grouped about a meter distant from 2 lamps, the clothing being removed and the eyes shaded. The patients were turned repeatedly, in order that the body might be thoroughly exposed to the light. Blood was obtained, the serum separated, treated with chloroform and refrigerated, and examined at the close of the treatment. For titration (Schroeder's method) a 24-hour broth culture was employed. The bacilli were killed with 0.001 dilution 40% formaldehyd and refrigerated for 4 days, being shaken daily. Decreasing amounts of serum were placed in test-tubes, normal saline added to 1 c.c. and then 1.5 c.c. of the broth culture. The tubes were shaken, incubated for 1 hour at 37° and left at room temperature for 24 hours before

reading. Each serum was first examined in dilutions of 0.1, 0.01, 0.001, etc. The final titration was made with 12 dilutions intervening between the 2 tubes of the preliminary test showing no agglutination and agglutination. The reciprocal of the dilution present in the tube just showing agglutination was used to express the agglutinin present. Time was plotted on the abscissa, agglutinin on the ordinate.

The light bath did not affect the period before the rise of the curve, which occurred 5 to 7 days after injection. In 4 cases, the normal curve-peak was replaced by a plateau, in 4 there was a slow decline and in 6 a second rise after beginning of the fall. The curve was thus altered in 14 of the 23 cases. The light bath proves either to increase the agglutinins in the blood or to diminish the rapidity of their usual decrease. Specimen curves are given. The effect depends on the duration and frequency of the bath. It is probably due to heating of the blood. During the war, it was shown that agglutinins produced by vaccination against typhoid were increased by infection with another febrile disease or by chemicals raising the temperature. The results here reported do not necessarily hold good for tuberculosis, although the antibodies of tuberculosis are probably affected by the light bath.

Further tests were made with 2 series of rabbits. In the first, 2 white and 4 colored rabbits were injected intravenously with killed typhoid bacilli, 3 receiving each 1 c.c. broth culture, 3 each 0.5 vaccine. In the second series, 2 colored and 4 white animals were injected intravenously with 0.5 c.c. vaccine each. The hair was removed with a depilatory mixture. A 50-ampère arc lamp was employed, the ray temperature being 30° C. At a distance of about a meter from the lamp, the 6 white rabbits were exposed to unfiltered light 2 hours daily for 6 days per week, the period of the test being about 1 month. The light bath produced a temperature rise of 0.5° to 1°. About 3 c.c. blood was taken from all the animals 3 times a week. The weight of all the animals diminished after injection. The controls then began to die, the light-treated animals to regain weight. The 6 controls died in 6-20 days; 1 test rabbit died during depilation, 4 survived the injection by 2 months, 1 by 27 days. No symptoms occurred and autopsies showed no changes. The tests are not fully conclusive. Some modification of the agglutinin curves must be attributed to venesection. The unusually early deaths were probably due to a specially toxic strain of bacilli. The tests indicate that light protects against the typhoid toxin, agreeing with Sonne's tests with diphtheria toxin. It is not yet proven whether the effect is produced by heating of the blood.

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**Etiology of Yellow Fever. XIV. Duration of the Protective Effect of Anti-Icteroides Immune Serum after Subcutaneous Inoculation into Animals.**

*Hideyo Noguchi, J. Exper. Med., 36: 357, Sept. 1, 1922.*

In these experiments guinea-pigs were used to determine the duration of the protective effect of an injection of anti-icteroides immune serum. Six different doses of immune serum (0.00001, 0.0001, 0.001, 0.01, 0.1, and 1 c.c.) were injected subcutaneously into 6 sets (2 each)

of guinea-pigs of about 500 gm. body weight. The tests for the persistence of passive immunity were made 1, 2, 3, 4, 5, 7, 10, and 15 days after inoculation of the immune serum. The infective material used was an emulsion of the liver and kidneys of a guinea-pig fatally infected with a strain of *Leptospira icteroides*, 0.1 c.c. of the emulsion, representing about 100 M.L.D., being given subcutaneously.

There was no diminution in protective effect within 48 hours, but after 3, 4, and 5 days 0.0001 c.c. no longer gave complete protection, while 0.001 c.c. protected in every instance. Seven days after injection of serum 0.001 c.c. failed to protect, while 0.01 c.c. was still effective. After a lapse of 10 days 0.1 c.c. was required to prevent infection, and after 15 days only those animals which had received 1 c.c. immune serum withstood infection. The rate of disappearance of the immune substance is very slow at first, but becomes rapid after about 10 days. Perhaps the sudden disappearance of immune substance after this period may be intimately connected with the precipitin formation for the heterologous anti-icteroides horse serum. Moreover, the titer of the immune serum suffers reduction when kept at 39° C., even in vitro, and may be expected to undergo similar reduction in the blood of a foreign species.

Applying these experimental results to man, for a man weighing 80 kilograms, 0.16 c.c. immune serum would theoretically be sufficient to protect for at least 5 days, 1.6 c.c. for 7 days, and 16 c.c. for 10 days. This temporary protection against yellow fever may be a valuable antecedent to that furnished by vaccination with *L. icteroides*, since the final effect of the latter cannot be expected until at least 9-10 days have passed.

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## **The Influence of Age and Temperature on Bacterial Vaccines. II.**

*W. F. Harvey and K. R. K. Iyengar, Indian J. M. Res., Calcutta, 10: 192, July, 1922.*

Experiments were performed to test the protection against *Bacillus avisepcticus*, the organism of fowl cholera, afforded by vaccines. Pigeons were used in the tests. The value of the protective vaccine was tested 0, 30, 60, 90, 120, 150, 180, 270, 360, and 450 days following the preparation. The vaccine was stored at room temperature, varying from 10° to 20° C., and at 37° C., the latter corresponding to the temperature common in India for considerable periods. The test antigen and the living organisms were administered intravenously. A standardized suspension of the organism in 0.85% salt solution was subjected to a temperature of 56° C. for 20 minutes, and 0.5% phenol was added as a preservative. The immunizing doses were 0.35 and 0.7 mg. desiccated bacterial substance, the second being given after an interval of 7 days. The test dose of living organisms, given 12 days following the second immunizing dose, ranged from 0.000,000,000,1 mg. to 0.000,001 mg. The real test of the protective effect was best obtained for immunized pigeons by dosages of 0.000,000,005 mg. and 0.000,000,5 mg. The observation time covered 96 hours. In addition to the protective power, the agglutination response in the pigeon obtained with the vaccine at



various intervals, and also the turbidity of the vaccine at the same intervals, were investigated.

The fresh vaccine protected rather less efficiently than vaccines 30, 90, 120, 150, 180, and 270 days old, but more efficiently than those aged 360 and 450 days. Little deterioration of the vaccine due to aging is noticeable up to the ninth month. The results for the vaccine kept at room temperature are only slightly more favorable than for those kept at 37° C. Even at 15 months there are many survivals among inoculated animals as compared with uninoculated controls. The fatality among the control animals remained constant throughout the 15 months.

After the agglutination had settled down, by the thirtieth or sixtieth day after the inoculation, it did not diminish for the remainder of the observation period. No marked difference was noted in the effect produced by vaccines kept at room temperature over that produced by vaccines kept at 37° C. Therefore the agglutinin content of the blood cannot be taken as an index to the degree of protection afforded by inoculation, since the protection afforded by antigens diminished by the twelfth or fifteenth month. However, it cannot be supposed that persistence of the agglutination effect has no relation to immunity. It may be that the antigen which has lost its protective power, due to age or exposure to high temperature, would, if combined with a small amount of fresh antigen, regain full power.

The tests of turbidity revealed no significant change in the vaccine kept at room temperature or at incubation temperature (37° C.), during the entire observation period. There is therefore no evidence of autolysis of the fowl cholera vaccine which has been killed by heat, and to which phenol has been added. Results were the same for *Bacillus typhosus* vaccine. Thus the turbidity is no certain indication of the protective power of an antigen.

These findings with *B. avisepticus* may not be transferable to other organisms, especially as the intravenous and not the usual subcutaneous method was employed. From these tests, however, it may be concluded that fowl cholera vaccine does not deteriorate, as regards its antigenic potency, with age or with subjection to any temperature to which it is likely to be exposed, within 6-9 months from the date of preparation.

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**The Influence of the Amino-Acids Derived from Decomposition of Bacterial Proteins in the Phenomena of Immunity.**

*Roberto Cárcamo, Semana méd., Buenos Aires, 29: 150, July 20, 1922.*

It is possible to prepare protein solutions which act immediately on injection, without danger of anaphylaxis. The substances which exert this immunizing effect are not the proteins themselves, but the products of their decomposition. These strengthen the natural defenses of the body; they do not introduce new antibodies, but stimulate the formation of protective elements. This is the basis for the preparation of antitoxic biosins. These biosins not only produce an immediate effect, but persist in their action for several months. This explains the violent and injurious effect of repeated large doses of vaccine, such as are frequently administered. The biosins contain proteins disintegrated in such a

manner that their antigens are ready for immediate action, and the amino-acids are capable of stimulating the metabolic reactions of the body. Cure of the disease is not immediate, especially in the case of obstinate tuberculous lesions, but in infectious and toxic disease the biosins are of both prophylactic and curative value.

The first effect of treatment is a sensation of euphoria and equilibrium, and the relief of digestive, intestinal, and other organic dysfunction. The hormones are stimulated, and toxic symptoms alleviated.

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**The Effect of Nonspecific and Specific Stimuli on Protein Catabolism in the Liver.**

*Bieling, Gottschalk and Isaac, Klin. Wchnschr., Berlin, 1:1560, July 29, 1922.*

After the subcutaneous and intraperitoneal injection of caseosan and typhoid vaccine in guinea-pigs there is an increase of the non-coagulable albumin of the liver at the expense of the coagulable cell-albumin which begins within 12 hours and ends on the second day. This rise in protein catabolism occurs much more strongly in guinea-pigs who have been sensitized by very small doses of horse serum that have no other effect, provided the animals survive the shock. If an immune serum that has been obtained by treating a rabbit with guinea-pig cells is injected into a guinea-pig, small doses of the immune serum produce a shock; in this reversed anaphylaxis also, a rise of protein catabolism can be brought about with hemolytic serum which may cause necroses in the liver. In guinea-pigs infected with tubercle bacilli small doses of tuberculin increase the protein catabolism of the liver after 12-14 hours. A change in the proportion, which is constant under normal conditions, of noncoagulable albumin to total albumin, gives an objective measure of the effect of proteins on certain liver functions.

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**The Influence of Protein Injections on the Complement Titer.**

*Karl von Angerer, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:25, May 24, 1922.*

Hoffman stated that the stabile agglutinin titer is not influenced by nonspecific protein. It is now found that in rabbits no change of complement occurs, from which it appears that neither the complement nor agglutinin titer is changed by foreign protein injections.

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**The Course of the Total and the Cellular Gas Metabolism during Anaphylactic Shock.**

*Emil Abderhalden and Ernst Wertheimer, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:487, July 21, 1922.*

The study of the body temperature of pigeons which had acquired alimentary dystrophy from being fed with polished rice and of those

which had been injected with adrenalin indicated the possibility of adding to our knowledge concerning the fall of temperature during anaphylactic shock. Guinea-pigs were used to study gas metabolism and tissue respiration, the latter with the aid of Bancroft's apparatus. Gas metabolism being much more energetic in young animals, it is important to use guinea-pigs of the same age. Tests were made in normal animals at the time of the first injection, of the reinjection, and during anaphylactic shock. The total gas metabolism diminishes during the stage of shock. This is not at first surprising when the severe dyspnea is considered; yet this does not explain it, since the greatest reduction of gas metabolism takes place after the severest symptoms of dyspnea have passed. Vasomotor paralysis cannot be held responsible, owing to its inconstant occurrence. In all cases, respiration was much reduced, and the addition of yeast preparations to the diet did not materially improve it. In this it differs from the course of alimentary dystrophy, particularly during the stage of spasm. Evidently in anaphylactic shock, we are dealing with a disturbance affecting all body cells. Because of its sudden onset, it cannot be explained from a decrease of substances which promote oxidation in the cells. Possibly the cause lies in an interference with the central apparatus. Further tests are planned to determine this.

If a diminution of tissue respiration could be shown to occur regularly in anaphylactic shock, this would furnish us with the means of determining whether the various phenomena of shock are or are not identical with anaphylactic shock (among them the symptom of shock following the introduction of nitrogen-free starch or agar, according to K. Schmidt).

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### **Anaphylaxis in Tuberculosis.**

*St. Somogyi, Beitr. z. Klin. d. Tuberk., Berlin, 52:170, July 28, 1922.*

Galambos, Friedberger and Gröbler concluded, from the fact that vagus paralysis and irritation of the sympathetic may prevent the anaphylactic reaction, that the anaphylatoxins act on the central nervous system and thereby bring about the anaphylactic reaction. They made the following observations: (1) In normal animals, that is, animals not infected with tuberculosis, a tuberculin hypersensitiveness could not be caused by a preliminary treatment with tuberculin alone. (2) Tuberculin hypersensitiveness could not be transmitted to a healthy animal by the serum of a tuberculin-hypersensitive animal. The 2 cases have in common that no opportunity had been previously given in them for the formation of a specific tuberculous focus. But Bail and Onaka succeeded in transmitting tuberculin hypersensitiveness by injection of tuberculous tissue. Ritter could not find a single case that reacted positively to tuberculin in vivo that did not show tuberculous foci on section, but he comes to a different conclusion.

The symptoms of general reaction are caused by the presence of a reflex arc whose centripetal branch leads from the focus to the central nervous system and whose centrifugal branch is the vagus. The anaphylactic reaction is the reflex of those focal reactions which are

caused by the acutely increasing inflammatory processes brought about at the periphery of the focus by the influence of extratubercular toxins. Where there is a general reaction there must be a focal reaction, but, on the other hand, a focal reaction does not necessarily cause a general reaction. A vicious circle is produced by the fact that in toxemia the toxin concentration of the blood when it increases also intensifies the extratuberculous toxin action, which may lead to severe toxemia until the reaction which brings about the production of antibodies becomes more pronounced. Allergy is the specific reflex sensibility of the organism, the physiologico-anatomic foundation of which is the specific focus developed in an earlier infection. Anaphylaxis is the symptom complex and allergy is its diagnosis.

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**The Protective and Curative Influence of the Incubator on Protein Disintegration Poisoning and Similar Conditions.**

*Hermann Pfeiffer, Ztschr. f. d. ges. exper. Med., Berlin, 29:46, July 21, 1922.*

It was found that parenteral disintegration and any autolysis of living protein, as e. g. in consequence of photodynamic action of light, or scalding, and further the entrance of protein elements into the circulation (peptone poisoning, total exclusion of the kidneys) produce a pathologic picture similar to anaphylactic shock, with a sudden decided fall of the temperature representing the principal phenomenon. The author proposed to determine by means of artificial nutrition in the incubator whether the severe general phenomena are a consequence of the drop in temperature incidental to so-called "cold narcosis."

(1) Effect of the incubator on the photodynamic disease of white mice: The mice were sensitized by injection of Bengal rose, which is otherwise innocuous, and then exposed to sunlight during spring and fall; during summer, the animals perished in consequence of overheating during the exposure. If the animal has been exposed until its temperature reaches 40° C. and has then been kept in the dark for 1-2 hours, a fall in its temperature of 4° may be considered as certain evidence that a lethal (if untreated) dose of insolation has been attained; otherwise the exposure should be repeated. If rabbits lethally insolated are placed in an incubator with a temperature of 32-35° C. in the lower and of 37° C. in the upper portion, it is possible, by cautious application of heat, not only to arrest the typical frigoriom, but also all other phenomena. These phenomena represent a condition similar to inebriation (with a body temperature of 25°, leading to tonic rigor and apnea), followed by a gradual fall of the temperature to 15-9° C., cyanosis and death through arrest of respiration; in addition, there is leukopenia and incoagulability of the blood. In other words, the photodynamic injury may be prevented by the cautious application of heat, so that the animals remain in good health for weeks. Even if a severe affection has already resulted, it can be cured, if the treatment is applied in time. But if caution is neglected in the application of heat, the animals become dyspneic and die, as if struck by lightning, before the untreated controls. Animals that have been protected

against or cured of the effects of insolation by this treatment, may feel well for several days and then suffer a "secondary" attack, manifested by the same symptoms, in consequence of renewed failure of heat regulation. Even a case that has already reached the agonal stage, may be cured by the incubator. The secondary attacks may recur several times. The suprarenal capsules of animals that succumbed to a secondary attack were found deficient in lipoids and chromaffine substance.

(2) Effect of the incubator on general thermal injury: Lethal burns (cauterization) produce the same aspect of poisoning in mice as does insolation and may be prevented or cured in the same way by the incubator. Rats lethally injured by scalding of the skin can also be cured in the incubator; but prophylaxis was unsuccessful in scalded rats which were first kept warm and then transferred to room temperature. Scalded rabbits died quickly of suffocation in the incubator, although no fall in temperature occurred and no benumbedness was present.

(3) Effect of the incubator on trypsin poisoning in white mice: Trypsin poisoning (intraperitoneal or intravenous), the lethal effect of which does not set in until after some hours, produces exactly the same effect (complete paralysis of heat regulation) as the photodynamic injury, as has been shown by Kirchheim. To this observation may be added that there is also parallelism in the effects of the incubator treatment and the occurrence of the secondary attacks.

(4) Effect of the incubator on lethal antipyrin poisoning: White mice treated with antipyrin in doses just barely lethal died after some hours under the aspect of cold narcosis. After doses several times as large, death ensued under paralysis of the respiration and clonic spasms. Against the symptoms of excessive chilling, the incubator has a curative and also a prophylactic effect. On the other hand, the spastic effect and the respiratory paralysis may be exacerbated and accelerated by the application of heat, so that animals that would not die of cold narcosis until after some hours at room temperature, sometimes die more rapidly of asphyxia in the incubator.

(5) Effect of the incubator in lethal exposure to cold and in spontaneous paralysis of heat regulation in white mice: The pathologic picture produced in mice by passive excessive chilling is the same as toxic paralysis of heat regulation and is influenced by the incubator in the same way. The same holds true of a comparatively frequent spontaneous affection of white mice, presenting the phenomena of "cold narcosis."

(6) Summary and conclusions: The results show that, in all these intoxications, "cold narcosis" forms the principal basis of all the other phenomena. The heat economy is at first deprived of the counterregulation against excessive chilling, while overheating is averted under intensive acceleration of the respiration. Then the respiratory regulation is affected, independently of the "cold narcosis." In the case of poisons causing collapse (amylene hydrate), the drop in temperature is not caused by primary paralysis of heat regulation but by circulatory paralysis; it is therefore natural that the incubator is ineffective. The point of attack of the poisons is the heat regulation center itself, as has been demonstrated with respect to anaphylactic shock (Hashimoto) and antipyrin. The secondary attack, observed



especially in cases of photodynamic injury and trypsin poisoning, shows that heat counteracts only the consequences of the "cold narcosis," but not the poison circulating in the body, which paralyzes the heat-center. Probably, fermentative processes play a part (in conformity with anaphylactic shock). The changes in the suprarenal capsules are only secondary. A therapeutic action on severe burns in man is not to be expected from artificial heat application, since the phenomena of cooling play a decisive part only in small animals, owing to their relatively large surface area. Even in guinea-pigs, the respiratory disturbances play a more important part. Still, the application of heat might be serviceable in borderline cases of burns less severe than those treated in these experiments.

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### **Complement Fixation in Typhoid Fever.**

*L. G. Hadjopoulos, J. Infect. Dis., 31:226, Sept., 1922.*

A simple differential quantitative technic for active serum complement fixation has been used successfully in the diagnosis of syphilis, gonorrhea and tuberculosis, and its application to typhoid is described here. Human serum is used while fresh. After keeping the serum together with the clot for 24 hours it is separated by centrifugalization and distributed equally in 6 pairs of small test-tubes in doses of 0.01, 0.02, 0.03, 0.04, 0.05 and 0.10 c.c. respectively. The left-hand series of tubes receive 0.5 c.c. salt solution each, and serve as controls for the hemolytic value of the serum in question. The right-hand tubes receive 0.5 c.c. of the bacillary antigen each. The tubes are placed at 37° C. for 30 minutes and then 0.5 c.c. of 0.5% suspension of sensitized sheep cells are added to all. Readings are taken in 15-30 minutes or as soon as the complementary value shows a unit of hemolysis in 0.02 or 0.03 c.c. of serum. The success of the test depends mainly on the proper choice of antigen and it must be remembered that organisms belonging to the same species may be differentiated immunologically. As a nucleus for the antigen used here 8-10 typhoid vaccines from various sources were collected. Occasionally a case is found which gives a positive blood culture but a negative complement fixation. If the antigen is further enriched with such rare strains a very potent antigen may be developed capable of detecting at least 80% of cases in practically all stages of the disease, from the first to the fifth week. This technic has been applied to 50 cases of typhoid and over 100 control cases. The complement fixations were controlled by blood cultures and agglutination tests. From the results it is evident that in the course of typhoid infection the formation of complement-fixing antibodies is one of the earliest and most constant immune manifestations. The introduction of a differential quantitative active serum technic makes it possible to utilize this property for the diagnosis of typhoid fever with satisfactory results. In a limited number of cases the test has been repeated with inactive serum and found similarly satisfactory; use of the active serum, however, saves much time in the routine work of the test.

(1e—214)

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**The Effect of Inactivation by Heat on Guinea-Pig Complement and Human Serum.**

*Paul Hirsch and M. Liebers, Deutsch. med. Wchnschr., Leipsic, 48:936, July 14, 1922.*

In the inactivation of guinea-pig complement by shaking or addition of cobra venom, there is a turbidity caused by the precipitation of globulin. (P. Schmidt, Liebers.) The author studied guinea-pig and human serums undiluted and diluted to 1/10 with salt solution or water, after half an hour's heating at 56° C. or after shaking, and found that after inactivation by heating they were clearer than after shaking. Moreover the refraction increases, not as measured by the refractometer, but only by Löwes interferometer. Examination with Siedentopf's slit ultramicroscope showed that after heat inactivation the larger ultramicro complexes were broken up into smaller ones; therefore it was not a question of a preliminary stage of heat coagulation. Examination by the new indicator method of Michaelis showed a decrease of acidity after inactivation. Löwe's new Tyndall photometer showed a decrease of the Tyndall phenomenon in inactivated serum, even when the change in the degree of turbidity of the dilution of serum in salt solution was hardly visible macroscopically. With this method of examination the precipitation was greater with Wassermann positive serums than with Wassermann negative ones; while with former methods of examination Wassermann positive and Wassermann negative serums behaved in about the same way.

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**The Nature of Heterogenetic Precipitin.**

*Friedberger and Lasnitzki, Klin. Wchnschr., Berlin, 1:1607, Aug. 5, 1922.*

The precipitates produced by homologous protein are distinguished from those produced by heterogenetic protein not only morphologically, but probably also chemically; the former are probably albumin precipitations, the latter lipid precipitations. By treating the components of the reaction with ether, which is a lipid solvent, the isogenetic precipitate was not affected. The heterogenetic precipitate however failed to appear at all, and on preliminary treatment of only one component with ether the reaction was weaker; its lipid character is therefore demonstrated.

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**A Study of Certain Protein Precipitants.**

*Alma Hiller and Donald D. Van Slyke, J. Biol. Chem., 53:253, Aug., 1922.*

The authors report the results of an attempt to ascertain empirically the manner in which some protein precipitants act toward the proteins and protein derivatives of blood, and of Witte's peptone as a representative mixture of intermediate products. The relative proportions of total nitrogen precipitated, and of the total nitrogen, amino-nitrogen, and peptid-bound nitrogen in the filtrates were studied with

colloidal iron, tungstic acid, trichloracetic acid (2.5%, 5.0% and 10%), alcohol, metaphosphoric acid, picric acid and mercuric chlorid.

From the results with Witte's peptone it appears that tungstic acid and picric acid are distinguished by the relative completeness with which they precipitate protein intermediate products, without precipitating amino-acids. Trichloracetic acid, however, permitted nearly all of these products to pass into the filtrate. It would appear that trichloracetic acid is especially fitted for use with solutions of partially digested proteins when it is desired to remove the proteins and to regain in their filtrates not only the amino-acids, but also a maximum proportion of the intermediate products such as albumoses and peptones. Tungstic and picric acids are better fitted for experiments in which it is desired to precipitate the intermediate products as completely as possible. Alcohol behaved toward Witte's peptone like tungstic and picric acids, but the authors found it to be an unsuitable precipitant for quantitative work. Metaphosphoric acid, colloidal iron, and mercuric chlorid are intermediate between trichloracetic acid and tungstic acid in the completeness with which they precipitate the intermediate products of Witte's peptone. All the precipitants employed were found to remove the blood proteins completely from ox blood.

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**Horse and Beef Hearts as Material for the Preparation of Extracts for Flocculation Reactions.**

*H. Felke, Deutsch. med. Wchnschr., Leipsic, 48:1097, Aug. 18, 1922.*

While Meinicke used horse hearts for the above purpose, extracts of beef hearts have been used for the Sachs-Georgi reaction. Sachs suggests the question whether there is any essential difference between the two. The author answers this question in the negative; he shows that an excellent extract for the Sachs-Georgi reaction can be prepared by following Sachs-Georgi's directions from horse hearts, and a very good extract for the Meinicke III reaction from beef hearts. There is no essential difference.

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**The Meistagmin Reaction.**

*Willis E. Gouwens, J. Infect. Dis., 31:237, Sept., 1922.*

The meistagmin reaction is a phenomenon which involves a lowering of the surface tension during incubation, when a diluted serum containing certain antibodies is mixed with its specific lipoid containing antigen. In this work more than 1100 tests were made in a study of the meistagmin reaction, using almost 200 different mixtures of rabbit serum and antigen. The serum was obtained from animals immunized against *Bacillus paratyphosus b.*, and the antigens were prepared from the homologous and several heterologous organisms, and from the liver of a healthy *B. paratyphosus b.* immune rabbit. The spontaneous surface tension changes and the limits of experimental error are as great when relatively dilute serum is employed in the test as when the

serum is diluted 1:20. Serum more dilute than 1:1000 shows a smaller degree of, and a slower rate of, spontaneous surface tension than lower dilutions. These facts apply to normal as well as immune serums. The substance in the antigen-serum mixtures which is responsible for relatively large experimental error is the blood serum, as measurements on the various other substances used in these mixtures gave constant and accurate readings. The Du Nouy surface tension apparatus gives readings with the biochemic mixtures employed, which are as accurate as those obtainable with the more cumbersome and slow drop weight apparatus. The sources of error are less than those involved in the use of the Traube stalagmometer. The meiotagmin reaction does not reveal the presence of antibodies in *B. paratyphosus* b. immune rabbit serum of high titer regardless of the dilutions in which the serums and antigens are employed, and of the solvents used in the preparation of the antigen.

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**The Value of the Refractoviscosimetric Properties of the Blood Serum in Cancer.**

*Max E. Bircher, J. Lab. & Clin. Med., 7:660, Aug., 1922.*

Previous studies on the blood of luetic patients showed that there is a definite decrease in the refractoviscosimetric quotient, which is attributable to an increase in the serum globulin. Similar studies in cancer are presented in this paper. The refractive and the viscosimetric index of serum can be determined with great accuracy. The quotient of refractivity and viscosity can be obtained as follows: For convenience the refractive index is expressed in Pulfrich's units. These are multiplied by 10 and divided by the viscosimetric index.

Example:  $\frac{56.0 \times 10}{1.75} = 320$ . Under physiologic conditions the variation of refractivity and of viscosity is very slight, as judged from the serum of healthy persons examined over a period of 6 months. The refractivity varied from 52.9-55.3, and the viscosity from 1.61-1.67, with an average of 1.64. The average refractoviscosimetric quotient is 331. The ratio of albumin to globulin, as determined by Naegeli's chart, shows an average value of from 60-40 and is within physiologic limits.

The results of 15 tests demonstrate the fact that the blood of women with benign tumors is not affected. Refractivity and viscosity were within normal limits with 1 or 2 exceptions. The refractoviscosimetric quotient ranged from 318-337, with an average of 328. The globulin was generally below 50% and rose slightly above it in 3 cases. This may be considered as normal. In marked contrast were the findings in malignant cases. The refractivity remained normal, while the viscosity of the serum was, as a rule, increased. Consequently the refractoviscosimetric quotient was decreased. The average was 307. The globulin percentage was decidedly increased, the average being between 60 and 70. Malignancy in any organ affects the refractoviscosimetric quotient in the same manner. It is markedly decreased.

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**An Electrochemical Study of the Condition of Several Electrolytes in the Blood.**

*B. S. Neuhausen and E. K. Marshall, Jr., J. Biol. Chem., 53:365, Aug., 1922.*

In this investigation an electrometric determination was made of the concentrations in the blood of sodium, chlorine and calcium ions; special electrodes were employed. A comparison of the ionic concentrations found with the total concentrations as determined by ordinary analytic methods indicates that the sodium and chloride are present as in an aqueous solution of sodium chloride (and sodium bicarbonate) of the same concentration, while only about 10% of the total calcium is present in ionic form.

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**The Water Content of the Blood at Various Periods of Life, Particularly in Infancy.**

*Elisabeth Grunewald and Erich Rominger, Klin. Wchnschr., Berlin, 1:1461, July 15, 1922.*

Refractometric determinations made twice daily in children showed a regular daily variation with a course similar to that of the body temperature from the second year of life on, and corresponding with an evening increase of the serum albumin; a simultaneous evening increase of weight was associated with it. That these daily variations are dependent upon muscular activity is shown by observations on the water of the blood of a nurse, who had a reversed type when on night duty, followed by a normal type after completion of night duty. Food had no effect on this curve.

Whereas in healthy children after the second year there was regularly thickening of the blood in the evening, infants have an irregular curve, which the author attributes to the incompleteness of the growing organism. As the irregular infantile curve is physiologic, pathologic deviations can be recognized only in extreme cases. Even in clinically distinct hydrolability, the curves showed no striking variations. Deviations from the normal in infancy are recognizable in cases of the severest pathologic thickening or its dilution (intoxication and nutritional injury from flour) of the blood by the absolute height of the concentration of the serum; the concentration of serum albumin increases with the age of the organism, beginning with fetal life.

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**The Relation between Age and the Concentration of Protein Fractions in the Blood of the Calf and Cow.**

*Paul E. Howe, J. Biol. Chem., 53:479, Aug., 1922.*

Howe has previously observed the variations in the quantities of certain protein fractions present in the blood of the new-born calf and the differences between the blood of young calves and of the adult cow. He now presents a study of the blood of 3 calves from birth to an age of approximately 2-3 months. Samples of blood were taken from other animals; 3 heifers 6 months old, 3 heifers 12 months



old, 15 virgin heifers 17-22 months old, and 14 pregnant heifers 2½ years old. These observations were supplemented by analyses of the blood of other animals for a short period and by data obtained in other studies. Of the calves which were studied continuously, one received colostrum of a high protein content, a second received colostrum which was comparatively poor in globulin, and a third did not receive colostrum, but was fed ordinary whole milk from birth. Blood was collected by needle from the jugular vein and when plasma was obtained coagulation was prevented by sodium citrate. Blood samples were taken 1 hour after feeding. The calves were fed ordinary whole milk for 1 month, after which they were given small amounts of grain and hay.

Determinations were made of total nitrogen, fibrin, or fibrinogen nitrogen, nitrogen content of the protein precipitated by concentrations of sodium sulphate of 14.2, 17.4, and 21.5%, and of the nonprotein nitrogen. From these determinations values were calculated for fibrin, euglobulin, pseudoglobulins I and II, and albumin, according to the procedures previously outlined by the author. The salient points brought out are: (1) During the first weeks of life the quantity of serum nitrogen present in the blood of young calves depends upon the quantitative nature of the diet just after birth. (2) In regard to the albumin nitrogen, the changes in the concentration of albumin, particularly in the first 3 weeks of life, do not appear to be correlated with the changes in the concentration of the globulins. (3) The determinations of fibrin on various young animals indicate a considerable individual variation and no relation of age to the fibrinogen concentration of the blood.

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**The Interrelationship of the Albumins and Globulins (Albuminous Quotient) in Serum and the Rohrer Technic.**

*Fred Wanner, Schweiz. med. Wchnschr., Basel, 52:785, Aug. 10, 1922.*

In spite of the advance in the efforts of determining the albumin-globulin interrelationship, especially since the use of the refractometer and viscosimeter, the aim of determining the protein bodies of the serum separately and to obtain a rapid method suitable for serial investigations has not been realized. The reliability of the newer method of Rohrer (1916), although it is used in such investigations, is doubted by the author on the basis of his own investigations. He denies the constancy of the albumin quotient and he believes that differences are demonstrated in the values in patients with edema in "dehydration" by experiments which are reproduced in several tables. He reaches the conclusions that the nonalbuminous substances have a greater effect on the refraction and viscosity than Rohrer assumes, and that the parallelism between the index of refraction and viscosity, which is almost constant in healthy persons, may vary markedly in various diseases. In the experiments of serum dilution with distilled water and concentrated salt solutions there is an error of 20% in the method.

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**The Determination of the Albumin-Globulin Interrelationship in Blood Serum.**

*Fritz Rohrer, Schweiz. med. Wchnschr., Basel, 52:789, Aug. 10, 1922.*

This article is essentially a reply to Wanner's article in the same number, questioning the reliability of Rohrer's method. The author disputes the validity of the serum dilution experiments of Wanner, as the prerequisite for Rohrer's method is absent, namely a constant relationship between the amount and the refracting portion of the non-albuminous portion of the serum. The limitations of this method have been mentioned before. These are the exceptional conditions in which the concentration of the noncolloidal substances are subjected to variations, as in uremia and hyperglycemia. Wanner's viscosity determinations are also affected by too great range of error to allow any definite conclusion against Rohrer's method.

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**The Amino-Nitrogen Content of the Blood Serum in Man.**

*Marcell Landsberg, Wien. Arch. f. inn. Med., 4:235, July 25, 1922.*

The Sørensen method was used to determine the amino-nitrogen while the albumin was determined refractometrically. The figure which is obtained by comparing the relation of the percentage of the serum albumin to the amino-nitrogen content is designated as the albumin quotient and it gives information regarding the structural condition of the serum albumin. Normally, the albumin quotient varies between 160 and 180; in hunger, the albumin quotient is higher than normal as an expression of a firmer constitution of the albuminous molecule. In a short period of infection, the albumin quotient is lower than normal (about 158), but in more protracted infectious diseases it rises as an expression of the inanition components. In serious diseases of the liver also, the albumin quotient rises. In pulmonary diseases (without fever) it is normal, but in cardiac diseases with edemas there is a rise. Nephritis and nephrosclerosis show a normal or reduced albumin quotient, but this is markedly increased in nephroses and rises with the increase of the edemas. In starvation edemas it rises above 200. In all conditions in which an increase of the globulin was determined, the albumin quotient was also higher, in accordance with the fact that the ratio between the globulin-protein quotient and the albumin-protein quotient is 362:210.

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**The Determination of Lactic Acid in Blood.**

*J. J. R. Macleod and M. E. Armour, J. Lab. & Clin. Med., 7:635, Aug., 1922.*

The authors record their experiences with the method of von Fürth and Charnass for determination of lactic acid in blood, with modifications introduced to avoid error. The method is inapplicable for urine examinations without very considerable modifications, and even with these the results were not entirely satisfactory. The present paper

details the method for determination of lactic acid in blood. With every precaution, and with precise standardization of the quantities of reagents used, the procedure is nevertheless fraught with many sources of error.

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**Micromethod for Qualitative and Quantitative Determination of Blood Fats.**

*Luigi Condorelli, Riforma med., Naples, 32:746, Aug. 7, 1922.*

Condorelli has employed Bang's technic for the determination of the fat content of blood, modifying it so as to render possible separate determinations of phosphatids and fatty acids as well as a direct estimation of free cholesterin. From a puncture in the ball of the finger 0.1 c.c. blood is removed by means of a finely graduated pipet (with graduation marks down to the point); this is smeared as thinly as possible over a rectangular piece of thin, porous cardboard which had previously been repeatedly washed in boiling water and freed of fat by immersion in boiling alcohol. The subsequent steps are outlined:

(1) Extraction and separation of neutral fats and cholesterin. Extraction is effected directly from the dried cardboard slide, by immersing it for 24 hours in a glass tube filled with petroleum ether. The slide is then dried by agitating in the air. The petroleum ether now contains in solution all free cholesterin and neutral fats. The ether is distilled off by placing the tube in a sand bath connected with a distillator; after completion of distillation there are placed in the tube several cubic centimeters of alcohol and 1-2 drops of 4% sodium hydroxid. The alcohol is evaporated off by boiling the tube contents to dryness—a procedure facilitated by placing within the large tube several glass capillary tubes, one of which is long enough to exceed the height of the column of fluid; drying is further insured by connection of the tube to a water vacuum pump. There are now introduced within the dried tube several cubic centimeters of petroleum ether, which are left for 24 hours; after this period of time the cholesterin is thoroughly diffused in the ether, which is decanted off and mixed with more petroleum ether that has been used for additional washing out of the tube walls. This ether now contains all the cholesterin, whereas on the tube walls there have been left the soaps (saponification of neutral fats); more petroleum ether is placed in the tube, followed by the addition of 4-5 drops of a 4% solution of sulphuric acid; this mixture is well shaken, the small capillary tubes being broken during the process by means of a glass rod. This mixture—to which is later added more petroleum ether that has been used for washing the tube wall—contains the fatty acids obtained by the action of sulphuric acid on the soaps.

(2) Determination of various individual lipid fractions—neutral fats, cholesterin, cholesterin ethers, soaps and fatty acids. The technic is the same for each fraction. To the quantity of petroleum ether containing one such lipid fraction there is added 1 c.c. of a 1% solution of sodium hydroxid, and the mixture is distilled until no more odor of petroleum ether can be perceived; then there are added 1 c.c. 0.1 n. chromic acid solution and 5 c.c. concentrated sulphuric acid (if at this point the solution assumes an emerald green color, it is an indication that the entire amount of chromic acid introduced has been utilized

and more must be added; if this additional quantity exceeds 2 c.c., then 2.5 c.c. sulphuric acid must be added as well); reduction is complete in fifteen minutes, the liquid portion is poured off, and enough distilled water is added to bring the volume up to 100 or 150 c.c., some of this distilled water having been previously used to wash the tube walls. After cooling of the solution, there are introduced 2 c.c. of a 5% potassium iodid solution, followed after some minutes by the addition of a few drops of starch water. The mixture is now titrated with a 0.1 n. solution of sodium thiosulphate until the blue color gives way to a light greenish tint, evidence of disappearance of all free iodine. By subtracting the amount of chromic acid introduced into the mixture from the amount of sodium thiosulphate solution used in the titration, one obtains the quantity of chromic acid which has been reduced by the fats in the mixture; this quantity is divided by 0.245, the quotient denoting the quantity of fats in the mixture expressed in tenths of a milligram.

(3) Extraction and separation of cholesterin ethers, soaps and fatty acids. The cardboard slide previously described, following drying after removal from petroleum ether, is extracted with acetone for 24 hours. The acetone is evaporated off by distillation until the mixture measures 0.5 c.c., when there are added a few cubic centimeters of alcohol and 1-2 drops of 25% sodium hydroxid solution. Capillary tubules are introduced into the large tube (as explained above), and the mixture is boiled in a sand bath for 5 hours. The entire fluid contents are evaporated off, desiccation being completed by means of the water vacuum pump; there are then introduced into the tube several cubic centimeters of petroleum ether, which, after 24 hours, will contain in solution all the cholesterin derived from the saponification of the cholesterin ethers. The soaps have remained in the tube, and are treated as described above, using, however, in this case a 25% solution of sulphuric acid instead of the 4% solution previously mentioned. The petroleum ether now contains the fatty acids derived (a) from the saponification of cholesterin ethers, (b) from previously existing fatty acids, and (c) from the soaps previously existing in the blood. The cholesterin derived from saponification of cholesterin ethers is estimated according to the procedure previously outlined; by dividing the figure obtained by 0.54 one obtains the quantity derived from ethers, the remainder being obtained from the fatty acids.

(4) Extraction and estimation of phosphatids. The cardboard slide, following exposure to acetone and drying, is extracted with alcohol for 24 hours. There are then added 2-3 drops of a 4% solution of sodium hydroxid, allowing 1 hour for saponification, after which one proceeds as outlined above for the neutral fats. Dividing the figure obtained by 0.63 reveals the amount of phosphatids present in the mixture (as distearin-lecithin).

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#### **A Method of Quantitative Cholesterin Determination in Blood Serum.**

*Michalski, Polska gaz. lek., Cracow, 1:653, Aug. 13, 1922.*

The method described by the author of determining free cholesterin in blood serum, requires only a small amount of reagents. It is sufficiently exact and can be carried out with as little as 2 c.c. serum.

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Digitonin possesses strong hemolytic properties even in a dilution of 1:12,000. Upon its addition to a solution of cholesterol in water or blood serum, it unites with cholesterol in equimolecular proportion. The uncombined excess digitonin hemolyzes sheep erythrocytes which are added to the digitonin-cholesterol mixture as indicator. If the amount of consumed digitonin is known, the amount of cholesterol contained in the experimental liquid can also be determined. As in Winelaus' method, the calculation is based on the combination of 1 molecule cholesterol with 1 molecule digitonin. Experimental procedure: each of a series of test-tubes receives 1 c.c. serum diluted 2, 5, 10, 20, etc., times with physiologic sodium chlorid solution. To each of these test-tubes 0.3 c.c. 1:1000 digitonin solution in warmed physiologic sodium chlorid solution are added. After thoroughly shaking the mixture, the test-tubes are placed 1 hour in the thermostat, whereupon 0.3 c.c. 10% suspension of well-washed sheep erythrocytes in physiologic sodium chlorid solution are added to each. Where an excess of uncombined digitonin exists, hemolysis takes place. That dilution in which barely commencing hemolysis is just detectable contains the cholesterol amount which has fully combined with the added digitonin.

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#### **Errors of Chlorin Determination by Bang's Micromethod.**

*Richard Prigge, Biochem. Ztschr., Berlin, 130:442, July 20, 1922.*

While some investigators consider this the most exact method of quantitative chlorin analysis in blood and serum, it is rejected by others. The following sources of error and means by which they may be lessened as much as possible are described. Errors of weighing are very small. Bang has stated that after completion of the chlorin extraction it suffices to pour a like amount of alcohol once more over the blood on the plate and to combine this extract with the first one in order to obtain the remaining chlorin. The author devised the following modification: In place of 16 x 26 blotting papers, those measuring 19 x 16 should be employed. These must be rounded off at the bottom to correspond to the curvature of the test-tube (internal diameter about 20 mm.).

Bang showed that when potassium chromate is employed as indicator in alcoholic solution, a distinct color change to brown takes place even on addition of extremely small amounts of silver nitrate (0.05-0.06 c.c. 0.01 n. silver nitrate) but only if the alcoholic filtered volume does not materially exceed 10 c.c. The author employed on an average about 100 mg. blood. With some practice the absorbent capacity of the blotting paper is learned quickly so that the correct amount of blood that will be absorbed is arrived at very closely. Only 5 c.c. alcohol are poured over the plates. After extraction is completed, the alcohol is poured into a filtering beaker and the plate is then extracted a second time. This liquid must not be poured off and united with the first one until 2 or 3 hours have passed. Following completion of titration, it then suffices to deduct 0.04 instead of 0.05 c.c. from the consumed amount of silver nitrate. In a supplement,



Bang suggests the use of very narrow test-tubes and after-washing with only 5 c.c. alcohol, thereby reducing the amount used.

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**The Distribution of Sodium, Potassium, Calcium and Magnesium between the Corpuscles and Serum of Human Blood.**

*Benjamin Kramer and Frederick F. Tisdall, J. Biol. Chem., 53:241, Aug., 1922.*

Employing standard methods, the authors have investigated the concentration of sodium, potassium, calcium and magnesium in the venous blood and serum of normal adults. The tabulated results show that human corpuscles are practically free of sodium. A study of 7 consecutive normal bloods showed practically no calcium in the corpuscles. The average concentration of potassium per 100 c.c. human corpuscles was found to be 428 mg. while the magnesium content of whole blood was found to vary from 2.3-4.0 mg. per 100 c.c. There is an excess of about 16% of basic radicles over the well-known acid radicles in both serum and corpuscles, which excess the authors believe is in combination with proteins. Sodium was found to represent about 92% of the fixed base of serum, potassium practically all that of corpuscles.

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**The Prosthetic Group of the Blood Pigment. Hematin.**

*W. Küster, Hoppe Seyler's Ztschr. f. physiol. Chem., Berlin, 121:121, July 29, 1922.*

The conversion of hemin into hematin is attended by transformation within the molecule. In the case of solution in a lye this transformation consists primarily in incorporation of water so that the iron detaches itself from the one nitrogen atom of a pyrrol nucleus, and secondarily in a cleavage of water in a different direction with deacidification. In a new preparation—dimethyl (bromo) hemin—the bromine could be entirely eliminated and the analysis of this dimethyl hemin yielded values agreeing with those calculated for a molecule richer in water. Strong lyes bring about a fundamental alteration in the hemin molecule, the action of pyridine merely causing replacement of the halogen by hydroxyl; dimethyl hydroxyhemin is formed which can be retransformed into the original substance. Another transformation takes place under the influence of alcoholic lye by the migration (in the case of methylester) of the methyl to the nitrogen, a pyrrol ring being produced from a pyrrolin ring and another pyrrol nucleus being transformed into a pyrrolin ring. Dimethyl (bromo) hemin was prepared experimentally from the part of a crude  $\beta$ -hemin insoluble in chloroform. The employed fraction represented a mixture of equal parts of monomethyl (bromo) hemin and bromohemin. There may be obtained also a dimethylated hemin which was prepared from hemin and de(hydrohalogen)hemin. Dimethyl hemin has the externalities of hematin, forming amorphous, dark steel-blue pieces with a metallic luster. Dimethyl hematin is easily methylated in acid solution.

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**A Method for the Spectroscopic Examination of Hemoglobin in the Living Animal.**

*R. H. Kahn, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:361, July 21, 1922.*

The new method permits the demonstration of the deoxygenation of hemoglobin during suffocation and its renewed enrichment with oxygen in sufficient respiration, as well as the spectroscopic analysis of the circulating blood and other facts as to the relations of the organism to the oxygen content of blood.

An albino rabbit is fastened in the animal holder, and one of its eyes is dislocated and brought in front of the eyelids. This can be done without any injury whatever to the eye. The conjunctiva is anesthetized with cocain, and the cone of a Sachs transilluminating lamp is placed between the edge of the cornea and the eyeball. The eye will at once show a ruby red illumination. If the anesthesia is repeated and drying of the conjunctiva is prevented by the drop application of Ringer solution, the test may be prolonged for an hour or more. The red light proceeding from the eye is examined spectroscopically. If, in a curarized and tracheotomized animal, artificial respiration is suspended, the green between the two absorption bands of oxyhemoglobin begins to grow turbid in less than 30 seconds; it grows darker until, in 60-90 seconds the absorption spectrum of reduced hemoglobin is fully developed. If artificial respiration is then resumed, the green will reappear after 6 seconds.

If the arterial blood pressure is recorded at the same time, the relations between the circulatory function and the supply of oxygen can be conveniently studied. The first change of the oxyhemoglobin spectrum appears when the dyspneic increase in blood pressure sets in. The change from oxyhemoglobin to methemoglobin can also be studied by this method (intravenous injection of sodium nitrate).

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**The Law Governing the Distribution of Hemoglobin upon the Surface of the Erythrocytes.**

*K. Bürker, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:516, July 21, 1922.*

According to this law, no matter how great the variation between the mean absolute number of erythrocytes and the mean absolute hemoglobin content in man (and in some mammals tested), the surface unit of all these erythrocytes holds the approximately constant hemoglobin fraction of  $32 \times 10^{-14}$  gm. That is, in man and in other mammals, the mean absolute hemoglobin content of an erythrocyte is equal to the square of the diameter of the erythrocytes of the species. Tests have been carried out in dogs, pigs, rabbits, horses, cattle, sheep and goats (10 of each) of different races and both sexes. The number of erythrocytes and the amount of hemoglobin may vary considerably among members of a species, but the average values are quite constant. The variations are fairly high in dogs and pigs, very low in rabbits, cattle, horses, sheep and goats. The relation of the mean hemoglobin content of an erythrocyte to the surface unit can be calculated without

regard to the thickness of the erythrocytes. With the cells spread in a thin layer and dried, the formula for the surface is:  $2\left(\frac{d}{2}\right)^2 = 1.57d^2$  ( $d$  = diameter). If this surface value be taken as the basis for calculating Hb content, the aforesaid law is derived. The values of the constants vary only between 29 and 34.

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**Two New Methods of Fibrinogen Determination. Albumin Determination in Salt Plasma, with a Study of the Fitness of Serum for Quantitative Blood Examinations.**

*G. Leendertz and B. Gromelski, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:114, July 28, 1922.*

The indirect method of fibrinogen determination heretofore in use, by subtracting the serum albumin from the plasma and taking the remainder as the amount of fibrinogen, is inaccurate, as in spontaneous coagulation the serum contains varying amounts both of water and of chlorids which come from the blood-corpuscles. The amount of albumin is too low, and therefore the result too high. Only the serum taken from the plasma separately from the blood-corpuscles before coagulation fulfils all the necessary requirements. Formerly it was the custom to prevent coagulation by the addition of traces of hirudin. At present hirudin is hard to obtain and quantitative analytic methods are too complicated. The new methods are as follows: (1) By puncture of the ulnar vein, 2 paraffined centrifuge glasses are almost filled with blood and centrifuged for a short time at moderate speed. A quantity of plasma is removed and placed in a measuring glass containing 3.55% sodium citrate solution in proportion of 1 part of the latter to 5 of the plasma. The further determinations are made by means of the refractometer. As a considerable quantity of blood is necessary this method can be considered only for venous blood. (2) This method is suitable also for capillary blood. The latter is placed in isotonic (3.55%) sodium citrate solution in proportion of 4:1, is well mixed and left to sediment with the air excluded by means of paraffin. Then to 5 parts of citrated plasma is added about 1 part of a 1.5% solution of potassium chlorid, by which the action of the citrate is neutralized so that coagulation occurs. With the first method there is theoretically a possibility of 0.04-0.06% of error, as compared with 0.5% formerly. In the second method there is no source of error; and as it is suitable for capillary blood it is the preferable method.

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**Method of Determining Blood Coagulation Time.**

*W. Heubner and P. Rona, Biochem. Ztschr., Berlin, 140:463, July 20, 1922.*

To be correct, a method must yield a reliable and distinct end-point. A definite degree of coagulation must be established. Only the testing of the fluidity of the blood can furnish information. A definite degree of coagulation can be defined as that at which a slowly

flowing blood column just stops. The observation of the flow and stoppage is most easily made by means of a stop-cock pipet from which the blood is allowed to drop slowly. The level of the dropping liquid and the resistance met with by the outflow influence the coagulation time. Of importance also are the mechanical or chemical treatment of the blood, the variety of glass of which the apparatus is constructed and precautions against undue lowering of temperature. Alkali has a retarding influence on coagulation. The duration of venous congestion previous to blood collection and the temperature to which the blood is exposed between collection and coagulation are also important.

The authors' coagulometer consists of 4 glass parts, 2 being joined by a rubber tube and 2 being ground together. The most essential part is the dropping pipet. Further parts are the receiving vessel, the capillary attachment and a protective tube to prevent suction of dust into the narrowed part of the capillary attachment which would alter resistance. The vein is to be compressed only a very brief time and after collecting 5 c.c. blood by means of an air-tight syringe this should be emptied without delay into a porcelain dish, from which the blood is drawn into a dry and absolutely clean dropping pipet the stop-cock of which is then closed. The mean time between beginning and end of the filling of the pipet is noted as the beginning of the test. When coagulation is ended the time may be read off correctly to within a few seconds. Frisch and Starlinger recently described a similar method in which the beginning of coagulation is recognizable by means of a retained thread of fibrin, termination of coagulation being shown by stoppage of flow.

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**The Heat Coagulation Point of Blood Serum and Its Variations.**

*Mayer, Klin. Wchnschr., Berlin, 1:1693, Aug. 19, 1922.*

The author studied the question of whether the blood serum normally has a constant coagulation point, and whether in pathologic processes with certain changes in the chemistry of the serum, there are variations in it. He found the following method the best for the determination of the coagulation point of the blood serum and the most accurate in control experiments: A thin-walled, dry U-tube of 3 mm. lumen and containing about 0.2 c.c. serum is fastened with 2 rubber bands to the lower end of a thermometer and heated in a large water-bath (beaker glass). By moving the thermometer here and there and by constant stirring, a uniform heat is maintained in the water-bath, and the heating is so arranged that in  $2\frac{1}{2}$  minutes there is a rise of  $10^{\circ}$  C. from  $70^{\circ}$ , that is, the water-bath in the beginning must have a temperature of  $70^{\circ}$  and must immediately be heated still further; only under these conditions will a uniform coagulation point be found. The author designates as the coagulation point that temperature at which the serum which was previously freely movable in the U-tube, becomes immovable.

The great majority of the 50 serums examined had a coagulation point of from  $73.50^{\circ}$  to  $75.50^{\circ}$ . The author has never seen a coagulation point lower than  $73^{\circ}$ , but some serums showed a disproportionately

high coagulation point, up to  $91^{\circ}$ , and in 1 case coagulation had not taken place at  $98^{\circ}$ . These were serums in which changes in the protein content were to be expected from the clinical diagnosis and in which comparative refractometric examinations showed values below normal. All the serums with coagulation points between  $73.50^{\circ}$  and  $75.50^{\circ}$  had normal refractometric values. In 1 case of uremia, a normal coagulation point was found while the refractometric value was abnormally high; in such a case the determination of the coagulation point gives a better insight into the composition of the serum than the determination of the light refraction.

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**Researches on Alterations in Volume of Blood-Corpuscles in Solutions with Different Osmotic Pressure.**

*Richard Ege, Biochem. Ztschr., Berlin, 130:99, June 20, 1922.*

If the osmotic explanation of the blood-corpuscle as a Pfeffer's cell, whose volume is determined by the osmotic pressure of the external fluid, is correct, definite quantitative relations must exist between the osmotic pressure of the external fluid and the swelling of the blood-corpuscle. If, therefore, the blood-corpuscle is surrounded by a semi-permeable membrane its volume in fluids having different osmotic pressure must be governed by the van't Hoff-Boyle-Marriotte law:  $p_0V_0 = p_1V_1$ . This equation (1) is apparently not valid for blood-corpuscles when  $V$  represents the blood-corpuscle volume, and should be replaced by the following equation (2):  $p_0(V_0 - x) = p_1(V_1 - x)$ , where  $x$  denotes the volume of the disperse phase. The determination of the volume of the disperse phase ( $x$ ) was attempted in various ways and was found to be about 10% greater than the percentage by volume of the solid matter of the corpuscle. If the ascertained value of  $x$  is introduced into Equation 2 the blood-corpuscle volume calculated from this equation will agree exactly with that actually determined, from which it may also be concluded that the blood-corpuscle volume is determined by the external fluid's osmotic pressure. The slight deviations which occur find a probable explanation by assuming that there are alterations in the degree of dissociation and that the blood-corpuscle membrane is able to offer but slight resistance to swelling.

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**Researches on the Permeability of the Blood-Corpuscle Membrane for Electrolytes.**

*Richard Ege, Biochem. Ztschr., Berlin, 130:116, June 20, 1922.*

It is maintained that blood-corpuscles must be impermeable either to the cation or the anion of the common salts and that they therefore behave on the whole, as regards alterations in volume, as if they were impermeable to the salt as such. A series of salts was investigated in this respect. It was also desired to ascertain which of the 2 principal theories, the pore theory and the solubility theory, has the greater justification. According to the former, different membranes are perforated by pores of different diameter. The substances must pass through



these pores in order to penetrate the membranes. The velocity of permeability is determined by the size of the molecule and the diameter of the pore. Precipitated membranes are impermeable not only to the membrane-forming substances but for all substances the molecules of which are larger than the membrane's interstices. Overton's lipoid theory maintains that the essential condition for the capacity of a substance to penetrate a membrane is the degree of solubility of the respective substance in the membrane-forming substances. If the substance is insoluble in the membrane it is unable to penetrate the same. If it is soluble it will penetrate with a velocity depending on the degree of its solubility in the membrane. Although this theory appears to possess some justification, the pore theory need not be abandoned for that reason. Possibly the theory of hydration, according to which the ions are surrounded by a greater or lesser number of water molecules, may furnish a prospect of a compromise between the pore and solubility theories. The velocity of diffusion seems to depend to a certain extent on the number of ions so that the velocity is greater the smaller the number of ions, but exceptions to this rule exist. The swelling velocity of erythrocytes was measured in ammonium salt solutions on the strength of which the relative permeability velocity of a series of anions was calculated.

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**What Influence Have Diffusible Nonelectrolytes on the Volume of Blood-Corpuscles?**

*Richard Ege, Biochem. Ztschr., Berlin, 130:132, June 20, 1922.*

In order to determine whether the osmotic explanation is the correct one, urea and ethyl alcohol, i. e. diffusible nonelectrolytes, were allowed to act on blood-corpuscles. While blood-corpuscles are hemolyzed momentarily in pure urea solutions no hemolysis occurs when 10% urea is added to 0.9% sodium chlorid solution. Therefore urea possesses no specific action. Ethyl alcohol behaves the same as urea as it, too, has no action on the volume of blood-corpuscles. Hence, when diffusion equilibrium has set in, urea and ethyl alcohol do not influence the blood-corpuscle.

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**The Significance of Hydrogen-Ion Concentration for the Volume of Blood-Corpuscles.**

*Richard Ege, Biochem. Ztschr., Berlin, 130:136, June 20, 1922.*

Although blood-corpuscles behave like Pfeffer's cells, which are surrounded by membranes impermeable to cations and to other electrolytes, as also by membranes permeable to a very large number of anions and to individual nonelectrolytes, other factors influence the osmotic pressure of the internal fluid of the blood-corpuscle as well as that of the external fluid. To this category belong, first, alterations of the external fluid's hydrogen-ion concentration which exercise a very considerable influence on the blood-corpuscle volume. The greater the hydrogen-ion concentration of the solution (up to about pH5) the

greater is the blood-corpuscle volume; the smaller the former (up to pH10) the smaller is the volume. The swelling of the blood-corpuscle in an acid fluid follows the ordinary laws and is due to the increase of the osmotically active components which arises from the acid condition in the blood-corpuscle interior.

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**The Effect of Diluting Fluids on the Result in Counting Erythrocytes.**

*B. Behrens, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195: 266. July 4, 1922.*

The result of counting red blood-cells according to Thoma, is influenced by the rapidity of sedimentation of the corpuscles, which is a function of the hemoglobin content, as Marloff has shown. But it also depends on the diluting fluids used, and the present article deals with this factor. Such fluid must have certain characteristics: it must preserve the cells as much as possible and allow an even distribution of the same; it must not agglutinate them; it must prevent too rapid sedimentation by its density and viscosity, without, however, interfering with their deposition in the counting chamber. Its index of refraction must not be too great to render the ruling distinctly visible. It must keep well, must not froth on shaking, must not stick, and must permit an easy cleaning of pipets and counting chamber. In practice, its viscosity and density are especially important, since on them depends the sedimentation. Various fluids have been employed: (1) body fluids (serum, ascitic fluid, etc.), (2) simple or complex isotonic salt or cane-sugar solutions, (3) solutions containing a fixing agent (bichlorid, osmic acid, etc.), (5) dye solutions, (6) solutions containing substances which inhibit coagulation.

The author has examined fluids of Groups 2, 3, and 4, using tyrode solution and sodium chlorid 0.9% of Group 2, Hayem's solution of Group 3, and Krotkow's solution of Group 4. In addition to human erythrocytes, those of the frog, which sediment very rapidly, and those of the goat, which sediment very slowly, were used in these tests. The most nearly exact figures of the rapidity of sedimentation are obtained by observing the lowering of the corpuscles in a relatively wide glass cylinder; this observation should be continued as long as possible. At an even temperature the rate of sedimentation of erythrocytes in a definite medium is quite constant; it increases more quickly with a rising temperature than it falls with a lower temperature. The rate of sedimentation in Hayem's fluid is unexpectedly rapid, since the mercuric chlorid which it contains passes through the semi-permeable membrane and weights down the corpuscles. Since time is consumed in this process, the rate of sedimentation is not as rapid immediately after setting up the mixture as after the lapse of 24 hours. At the end of that time it is constant. Hemolysis occurs after 24 hours when isotonic salt solution or tyrode solution is used. Owing to its greater density, Krotkow's solution in a measure eliminates the systematic error of the Thoma method, but it causes human erythrocytes (and still more those of the goat) to coagulate, and renders the ruling of the counting chamber less clear. Bürker's method yields results which

are much more independent of the diluting fluid. Hayem's solution is still the best all-around diluent.

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**A New Histology of Red Blood-Corpuscles and Staining Technic.**

*E. L. Dewey, J. Indiana State M. A., 15:305, Sept. 15, 1922.*

The red blood-corpuscle is a very definitely organized structure composed of a central or supporting membrane, "the structureless, homogeneous mass," which is covered completely with very delicate membranous segments, individual and separated from each other by an intrasegmental membrane. The periphery of the corpuscle is surrounded with a delicate membrane which supports the peripheral segments. The peripheral membrane and the intrasegmental membrane take the basic stain. The peripheral segments are fairly uniform in size and arrangement, presenting a picture not unlike the cross section of an ear of corn, the kernels representing the peripheral segments. In the full size matured corpuscles, the number of these peripheral segments varies from 11-20 or more. In the small and young corpuscles, the writer has seen as few as 5 or 6. The segments which occupy the central stroma of the corpuscle are irregular in size and shape. In the young corpuscle there may be no central segments, or only 1 or 2, those of the periphery occupying the whole surface of the corpuscle. In from 80-85% of red blood-corpuscles, the segments all take a pale neutrophilic stain with a rather pinkish tint. The other percentages take a heavy basophilic stain with a metallic luster. In some corpuscles, this characteristic is manifested in all of the segments, central and peripheral, some only the peripheral segments, and others only the central segments; still others mixed, a portion of the central and of the peripheral segments basophilic, and others a segment or segments here and there, basophilic.

Dewey's blood stain technic is as follows: Place in a graduated bottle of 400 c.c. capacity these solutions in the order named—saturated aqueous solution eosin, W. S., 30 c.c.; saturated aqueous solution anilin violet, 60 c.c.; 1% aqueous solution sodium bicarbonate, 60 c.c. Place in a water-bath, the water of which comes to the level of the solution or a little above, and boil 30 minutes. Remove from water-bath and while still boiling hot, add 95% alcohol to 300 c.c. Shake well for a few minutes, set aside to cool, and filter. Dissolve the precipitate collected on the filter paper in 95% alcohol by rubbing up well in a mortar. Add to filtrate and enough more alcohol to bring the total volume up to 640 c.c. Add distilled water 80 c.c., and 40 drops of saturated alcoholic solution of anilin violet. Neutralize with 1% acetic acid solution; the amount to be used is determined by titration. Take 1% aqueous solution of sodium bicarbonate 600 c.c., place in a beaker and boil a few minutes to drive off the hydrogen atom and CO<sub>2</sub>. Add 3 volumes of water and 3 or 4 drops of phenolphthalein indicator. Titrate with 1% acetic acid solution until the solution shows only a very faint trace of the pink color. If tested now with litmus it will be found neutral. The buret reading will indicate the amount of 1% acetic acid solution which is now added to the stain; filter. This constitutes the stock to Dewey stain, and keeps indefinitely.

To 50 c.c. stock stain mix well 1% aqueous solution acetic acid 5 c.c., and 1% aqueous solution carbolic acid 5 c.c., and then filter. The stain is now ready for use. Use only distilled water in making solutions. Acetic acid solutions used should be titrated with 0.1 n. standardized solution of sodium hydroxid. Make the slides perfectly clean by washing in water and then in alcohol. Heat them over an alcohol flame or Bunsen burner until all moisture has disappeared. Allow them to cool. On the edge, near the distal end of a second slide, collect a small drop of blood, press it down, and drop the edge first on to the prepared slide until the drop is completely flattened. Separate the slides by a quick swipe in the long axis of the slide being smeared. Allow the smear to dry in the air at ordinary room temperature for 10 minutes. To fix the smear, immerse in Squibb's ether that has not been previously opened or used for an hour, remove from the ether, and allow to dry without washing. Immerse in Dewey's stain 2-10 hours, according to intensity desired. Beautiful and contrasting specimens are produced in 3-6 hours. If it is desired to study the blood platelets or leukocytes, the longer exposure is recommended. Wash the specimen in running water for 5 minutes; dry in the air at room temperature; immerse now in anilin oil water for 5 minutes. Remove and immediately plunge into a diluted solution of methyl-violet, wash in running water for 10 minutes, dry in the air at room temperature and mount in balsam in the usual way.

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#### **Lymphocyte Lipase.**

*S. Bergel, Biochem. Ztschr., Berlin, 130: 533, July 20, 1922.*

Nees investigated white leukocytes and attributed lipolytic capacity to them as well as to staphylococcus and streptococcus pus-containing leukocytes. The author considers umbilication on wax plates characteristic not only for tuberculous pus containing leukocytes but also for other kinds of pus. The reason for fat cleavage is that the hemolysins produced by staphylococci and streptococci and obtained from the bacterial culture filtrates prove strongly lipolytic, a behavior not shown by polymorphonuclear leukocytes. If such are to be investigated regarding lipolysis, exudates must be produced in the thoracic or abdominal cavity by means of casein or aleuronat injections and the massed leukocytes washed and allowed to act on wax plates. No umbilication takes place. The fat-splitting lymphocytes enter into active relations with the lipoferous tubercle bacilli. The significance of lymphocytes, as well as of lymphatic glands in which they are formed, in relation to tubercle bacilli, is to be regarded in the sense of a protective reaction.

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### **1f. PATHOLOGY**

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#### **The Theory of Inflammation.**

*Ferdinand Roeder, Wien. klin. Wchnschr., 35: 651, July 27, 1922.*

The inflammatory process shows exudative, alterative and proliferative phenomena. Virchow explains the latter as being due to formative stimulus by the agents which produce the inflammation; Weigert says that potential bioplastic energy is set free by relaxation of tension as a result of destruction of tissue constituents. The latter theory has no value as a working hypothesis and is to be rejected

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physically, as there can be no potential bioplastic energy; a potential energy cannot exist in a special form. The question is rather what source of energy is transformed into the special form of energy.

The author explains the tissue-forming activity of inflammation by compression; the elastic-tissue cells, by the inflammatory hyperemia and extravasation. The compression leads to a decrease in volume by pressure on the gas-forming phase present in the cells, and thereby to an increase in the concentration; the latter hastens the course of reaction within the cell. The increase of energy in the cell caused by this is, according to the author, the source of force for the cell proliferation. Hypertrophy from use of muscle serves to confirm this theory, as the muscles on increase of function always show local rises of capillary pressure; it is also confirmed by the necessity for heart hypertrophy in permanent rise of pressure. On the other hand, the author attributes the phenomena of decreased vitality in inflammation, that is the alteration of the vessel wall and the regressive tissue changes, to decrease of cell energy by a fall in capillary pressure. The phase of fall of capillary pressure follows the arterial hyperemia and ends with increase of tissue and capillary pressure as a result of exudation. There is enlargement of the cell as a result of decrease of pressure; the gas phases which inhibit the chemical interchange of the cell molecules become larger by expansion, and gas vacuoles are formed by confluence, which, when they reach the size of the wave-length of light, cause turbidity of the cell contents. Finally they rupture and in their place droplets of fat and lipoids appear. Because of decrease of endocellular energy, there is not sufficient defense against injurious action from without or against substances from within which fill the cell or produce coagulation, and so there is degeneration and necrosis. This theory is supported by the fact that only those protoplasm toxins produce cell degeneration which have a depressant effect on the circulation (chloroform, chloral hydrate, diphtheria toxin and typhoid toxin).

The injury of the vessel wall of the region by interruption of blood supply is not to be attributed, as was formerly believed, to lack of nutrition, but rather to the factor of fall of blood pressure. A stronger inflammatory irritation produces locally first paralysis of the constrictors and then of the dilators, with narrowing of the small arteries and thereby fall of capillary pressure with the above-described results. An effort at compensation is made: (1) by a general reaction and by fever (increase of the volume per minute); and (2) locally by compression of the veins by exudation. Inflammation, therefore, runs in 2 stages, that of quickening of the circulation and that of slowing of the circulation. The second more characteristic stage has 2 phases: fall and rise of capillary pressure.

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**Tissue-Specific and Nonspecific Stimuli and Their Relation to Inflammation.**

*Staemmler, Deutsch. med. Wchnschr., Leipsic, 48:966, July 14, 1922.*

Inflammation is the local reaction of the organism to stimuli which are not tissue-specific. Tissue-specific stimuli are those to which the body has become adjusted by inherited or acquired adaptation so that they are specific for certain tissues. The latter lead essentially, if



they are increased over the normal, to a hyperfunction. Not only do physiologically differentiated tissues react to the former, but all tissues which are locally accessible. The parenchyma is adapted to the frequent physiologic stimuli which are specifically adjusted and has, therefore, lost its reactive capacity to general, nonspecific stimuli. For this reason, it is usually less involved in reactive inflammation. The expression parenchymatous inflammation is, therefore, only justified when a reaction of the parenchyma is definitely shown. In many cases, the starting point of the inflammation can be demonstrated in a primary tissue injury (necroses). But often this is not the case, as, for example, in centrally caused inflammation of peripheral parts (the skin in herpes zoster). Not infrequently a certain habituation to pathologic stimuli can be seen, as, for example, in the action of the sun's rays on the skin; at first there is an inflammatory reaction but later only pigmentation. Stimuli which are ordinarily tissue-specific may under some circumstances (atavism), bring about nonspecific reactions. Such abnormalities seem to be due to certain idiosyncrasies.

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**The Significance of the Point of View in the Limitation of the Concept of Inflammation.**

*H. E. Hering, Münch. med. Wchnschr., 69:998, July 7, 1922.*

The various new definitions of inflammation are far removed from the old, which includes as the cardinal symptoms rubor, calor, dolor, tumor (exudation) and loss of function. The definitions vary in accordance with the clinical, pathologico-anatomic, or biologic point of view. Aschoff's definition from the biologic standpoint assumes inflammation to be the sum of the regulatory processes of the organism, demonstrable by clinical, morphologic and biologic methods, resulting from pathologic stimulations; according to Aschoff, this definition expresses the nature and not the characteristics of inflammation, but a useful definition should also mention the important characteristics, by which the thing defined may be recognized. Only such a definition is useful as combines the medical, clinical, pathologico-anatomic and biologic points of view. From the standpoint of the physician, which is an etiologic one, the author decides to define acute inflammation as the sum of the reactions which appear as the effects of pathologic coefficients in the form of vascular alterations of calor, rubor, tumor (exudation, emigration, proliferation) and the loss of function. From this point of view, the question of the benefit or harm of the individual reactions is immaterial from the standpoint of the investigator, but not so from the standpoint of the practicing physician. The inflammatory process must not be considered to be entirely uniform; the various tissue reactions should be evaluated, each on its own account, in regard to its purpose.

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**Removable Water-Bath Tops for Paraffin Embedding and Low Temperature Evaporation.**

*Oscar T. Schultz, J. Lab. & Clin. Med., 7:689, Aug., 1922.*

In 1917 Schultz described a rectangular electric water-bath for serologic work. The need having arisen for a bath for paraffin embedding, it appeared possible to devise a top which would transform the

serologic water-bath into a paraffin bath at a considerable saving of space. With this object in view, a removable top was made to fit the small  $9 \times 4\frac{1}{2} \times 5$  in. water-bath. The top is made of sheet copper and has 3 cylindric, sheet copper depressions,  $2\frac{3}{4}$  in. deep by  $2\frac{1}{4}$  in. in diameter, each of which holds a beaker of stock size. There are also 5 depressions  $1\frac{3}{4}$  in. deep by  $1\frac{5}{8}$  in. in diameter, which take wide-mouth vials or square-bottom test-tubes of standard sizes. A tubulature is provided for a thermometer. In addition to the paraffin bath top, there is a removable ring top which transforms the  $9 \times 9 \times 5$  in. serologic bath into a bath for evaporation of volatile fluids at low temperature. The top is made of sheet copper and has 2 openings  $2\frac{1}{2}$  inches in diameter, 1 opening 4 in. in diameter and 1 opening 5 in. in diameter. A series of concentric rings adjust the size of the opening as required.

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**Normal and Pathologic Histology of the Parathyroids.**

*Noodt, Virchow's Arch. f. path. Anat., Berlin, 238:262, June 14, 1922.*

The author distinguishes according to Cohn's classification: (1) compact, unarticulated parathyroids; (2) cordlike parathyroids; and (3) lobular parathyroids. The epithelial cells are divided into: (1) Water-clear cells resembling plant cells, with round, often eccentric, nuclei; and clear chief cells. (2) Rose-red cells with finely granular protoplasm and small, darkly staining nuclei; and dark chief cells. (3) Welsh's oxyphil cells. The parathyroids of 23 infants and 18 children older than 1 year were studied. It was found that there is not a characteristic structure for certain ages, although Ritter asserts that in new-born infants they are compact, in young individuals reticulate and in old age lobular. But with increasing age the compact structure becomes less dense. The most frequent type is the cordlike. In infants and young children, clear and dark chief cells were found, but never Welsh's cells; later the clear cells became rarer and the dark ones predominated in adults.

Colloid was seldom found in children, more frequently in adults. The author found it once in an infant and once (only a little colloid) in a child over a year old. Fat was always lacking in the epithelial cells in the first 4 weeks of life; in children, but not in adults, on staining with Sudan stain, red masses were often found near the vessels. In rickets, the author found (contrary to Ritter-Erdheim) neither frequent increase of connective tissue nor predominance of dark cells; in fact no variation from the normal. But in Möller-Barlow's disease the clear chief cells predominated and the cells were particularly large.

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**Pathologic Anatomy of Addison's Disease; Agenesis of the Left Suprarenal; Atrophy of the Medullary Substance as a Result of Hemorrhage from Venous Thrombosis of the Compensatorily Enlarged Right Suprarenal.**

*Veit, Virchow's Arch. f. path. Anat., Berlin, 238:269, June 14, 1922.*

After a discussion of the literature, the author gives a summary of the results: Heretofore only cases of right-sided congenital defect

of the suprarenal have been described (some of them in old age). Generally they are accompanied by other developmental disturbances (absence of the right kidney, displacements and inhibitions of development of the internal female genitalia). In one case there was compensatory hypertrophy of the left suprarenal. In all the other cases (6), Addison's disease had developed. After destruction of one suprarenal, compensatory hypertrophy of the other, or free parts of the interrenal system, occurs in man even at an advanced age. Exclusion of one suprarenal in animal experiments produces hypertrophy of the other only in young animals. The compensatory hypertrophy may extend to all layers, but is localized chiefly in the zona fasciculata. Acquired destruction of the suprarenal is mostly from contraction caused by old tuberculosis. Thrombosis of the suprarenal veins (generally marantic in nature) produces hemorrhages which generally cause only moderate degeneration of the parenchyma, but may also cause destruction of the whole organ. As a result of the peculiarity of the vessel distribution, the right side is generally thrombosed and usually Addison's disease does not develop; but there are cases of bilateral thrombosis with an acute course. The breaking down of medullary substance does not cause Addison's disease; only destruction of the detoxicating action of the cortex produces this result.

The author describes a case of congenital absence of the left suprarenal in a 50 year old woman. At the same time there was uterus bicornis with only slight development of the left horn; and deafness since childhood. The right suprarenal was hypertrophic (zona fasciculata). As a result of insufficiency of the heart (adiposity and callosity of the myocardium), there was marantic thrombosis in the vein of the hypertrophied right suprarenal. About 5 weeks before death, as a result of increase of the thrombosis, there was an extensive hemorrhage into the suprarenal. About this time the patient, who for 15 years had suffered from moderate cholelithiasis, noticed that she became yellow without any pain and that she was becoming more and more emaciated and losing strength. Then the signs of a rapidly progressive Addison's disease developed. Examination of the suprarenal showed the cause of this to be necroses in the cortex resulting from extension of the thrombus into the zona fasciculata. Death was caused by an erysipelas of the face which was slight in itself, but because of the poor condition of the patient it caused a peracute sepsis.

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(1f—88)

**Frequency and Localization of Cancer Metastases with Special Reference to Their Histologic Structure.**

*Kitain, Virchow's Arch. f. path. Anat., Berlin, 238:289, June 14, 1922.*

The author has made a detailed statistic study of 452 autopsied cancer cases with reference to metastases. He found no metastases in only 128 cases, which was due to the fact that he examined all nodules microscopically, even those that could not be recognized as carcinoma macroscopically. In 110 cases (11.5% of all the metastases), the diagnosis could only be made microscopically; 64 of the 128 cases without metastases were cases in which the primary tumor had been

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removed surgically; in 64 other cases of operative removal of the primary tumor, the number of metastases present was much less than in the nonoperated cases. Two factors may serve as an explanation of this fact: Retrogression of some nodules after removal of the tumor or earlier death after operation so that the patient did not live until extensive metastases had developed. The metastases were most frequently in the lymph-glands, next in the serous membranes; of the other organs, the liver showed the most frequent metastases (as a consequence of the greater frequency of the primary tumor in the region of the source of the portal vein); then follow lungs and bones; metastases are rarest in the pia mater, gall-bladder, bile-ducts, myocardium and endocardium, pharynx, larynx, vagina, prostate, testicles, epididymis, and ureters. Relatively frequent (in comparison with the figures of other statisticians) were metastases in the kidneys, suprarenals, intestine and ovaries.

Carcinomas of the thymus, breast, prostate, thyroid and lungs seem to show the greatest tendency to metastases in bone and bone-marrow. An important point in the relatively great number of metastases in the lungs is that it was here that the greatest number of metastases that could only be recognized microscopically were found. Among the primary localizations from which metastases are comparatively rare and when present not numerous, are the larynx, uterus, skin, bladder, intestine, upper jaw, pharynx and tongue. But on the other hand, tumors of the prostate, bile-ducts, pancreas, stomach, ovaries, breast, gall-bladder and bronchi show a special tendency to metastasize. In considering the different forms, the cancroids show the least tendency to metastasis; there is a greater tendency to metastasis in medullary cancer, then in adenocarcinoma, then follows scirrus, only 20% of which run their course without metastasis, and finally carcinoma simplex, in which there were always metastases. There is no decrease of the tendency to metastasis with increasing age up to the seventieth year, but after that it does seem to exist. It is doubtful whether this is due to lesser malignancy as a result of lesser vitality of the tissues; it may be partly due to the fact that the metastases are not survived, also to the fact that at more advanced ages the cancroids, which show less tendency to metastasis, are more frequent. The greater the development of the primary tumor at the original site, the more limited in general the development of metastases.

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(1f—89)

(1f—89)

**Giant Centrospheres in Xanthomatous Tumors.**

*David T. Smith, Bull. Johns Hopkins Hosp., 33: 342, Sept., 1922.*

Workers with tissue cultures have discovered a group of complicated but characteristic changes which take place in cells when they are beginning to degenerate. One of these signs is a marked swelling of the centrosphere, an area found around the centriole (centrosome). Swelling of the centrosphere or giant centrosphere produces the appearance of a clear area near the nucleus, often as large as the nucleus or even larger. Various granules, including pigment granules, when present are arranged in radiating lines arranged with the centriole as a center; in degenerating cells they retain the same relation to the

giant centrosphere. Of course in the fixed tissues of the pathologist the centrosphere cannot itself be seen, but in pigment-laden cells the centrosphere is indicated by the presence of a clear area about which the pigment granules are arranged radiatingly. By this means, Smith has discovered in about half his cases of xanthomatous tumors many cells showing enlargement of the centrosphere, indicating degeneration of the cells. In a large number of other pigmented tumors, including benign and malignant moles, giant-cell tumors of bone, and sarcomas of bone, a giant centrosphere was not seen. It is suggested that the application of refined cytologic knowledge and the modern technics to tumor cells might show many similar unsuspected abnormal conditions.

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(1f—90)

(1f—90)

**Presence of the Much Granules in Localized Surgical Tuberculosis and Their Significance.**

*F. M. Marras, Ann. d'igiene, Rome, 32:544, July, 1922.*

From researches carried out by the author it is found that the presence of the Much granules in certain lesions is of great importance, because in tuberculous material where it is not possible to find acid-fast bacilli by Ziehl's method, it is possible to diagnose a tuberculous affection in this way. In 14 cases, with material certainly tuberculous, where the typical Koch bacilli were absent, it was possible to demonstrate the Much granules. It is not possible to confuse these granules with cocci because they have certain special characteristics; they are larger and more refrangent. Considering then that the organism, in surgical tuberculosis, is probably resistant to the tuberculous infection, the circulation in the serum of the antibodies, at points less resistant where the infection is not entirely extinguished, would produce degeneration of the tubercle bacilli with loss of acid resistance and the formation of these granules or spores, capable, in certain conditions, of transforming themselves into typical forms stainable by Ziehl's method.

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(1f—91)

(1f—91)

**Experimental Diphtheria Infection in the Mouse. Histology of the Kidney Changes.**

*Wolff, Virchow's Arch. f. path. Anat., Berlin, 238:237, June 14, 1922.*

By infecting white mice with certain strains of diphtheria bacilli, a typical clinical picture can be produced, contrary to Löffler's original assertion but as has already been shown by Kolle and Schlossberger; its course depends essentially on the dosage. Its lesser sensitiveness as compared with the guinea-pig makes the mouse a more suitable experimental animal for comparison with man in regard to certain phenomena of diphtheria. Injection of a few large doses or numerous smaller doses of diphtheria toxin (toluene toxin Merck) produced the same symptoms as infection with diphtheria bacilli (the same strain was always used). The symptoms were cerebral in nature and localized in the corpus striatum, as shown by F. H. Lewy. The author studied particularly the anatomic changes in the kidneys. The general disease



in the mouse is always accompanied by an affection of the kidneys which varies in degree. In human diphtheria, the condition of the kidney shows great variations in the different epidemics. But just as uremia does not play any part in the clinical picture in human diphtheria, so the cerebral symptoms in the mouse have nothing to do with uremia.

Macroscopically the kidneys are often gray-white to gray-yellow, microscopically they show the different stages of nephrosis as in man; in severe intoxications, there are necroses; in milder intoxications, in addition to degeneration, there are regenerative processes.

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(1f—92)

(1f—92)

**The Histologic Foundation for Experimental Hyperkineses in Mice Infected with Diphtheria.**

*Lewy, Virchow's Arch. f. path. Anat., Berlin, 238:252, June 14, 1922.*

In mice which Wolff (preceding article) infected with suitable strains of diphtheria bacilli with a dosage from which the animals died on the fourth to the tenth day, hyperkinetic phenomena appeared between the third and tenth days. These phenomena were characterized by rapid alternation of hypertonic and hypotonic conditions. There was choreiform motor restlessness interrupted by sudden complete rigidity, a condition apparently related to mobile spasm. In the mice affected with this condition, changes were always found in the brain, always in the small neostriate elements, frequently in the central thalamus nucleus and often in the hypothalamus. These were peracute necrotic processes or less acute ones accompanied by a glia reaction, in which the reactive glia was also destroyed. The milder changes were in miliary foci, the severer ones distributed diffusely.

In subacute cases the cell processes were tingible for a long distance, just as in human chorea. The author had formerly produced, by manganese dioxid intoxication in rabbits, a peculiar rigidity of a plastic type and found in these animals also disease of the striatum, but of the large ganglion cells; while in diphtheria it was the small ones that were affected. There is, therefore, a specific affinity of certain toxins not only for certain nuclear regions but even for certain kinds of cells. The author lays the chief stress, however, on the possibility of the experimental production of a clinical picture that resembles human chorea symptomatically and with reference to anatomic localization and histologic changes.

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(1f—93)

**Heart and Vessel Changes in Experimental Diphtheria in the Guinea-Pig.**

*Tomojio Iwabuchi, Wien. klin. Wchnschr., 35:711, Aug. 24, 1922.*

The author examined 37 guinea-pigs which had died in the Vienna Serotherapeutic Institute after treatment with diphtheria toxin alone or a mixture of toxin-antitoxin. There was albuminous and fatty degeneration of the heart. The latter was lacking after 2 days' duration of the experiment in 5 out of 16 cases; after more than 2 days, in 7 out of 21 cases, and only in animals that had been treated with the toxin-antitoxin mixture; the fatty degeneration, therefore, seems to be dependent on an excess of toxin. Myolysis was never observed.

Among interstitial changes, there was almost always early dilatation of the capillaries and precapillaries (partial phenomena of a general vessel paralysis), often with striate interstitial hemorrhages. In addition to increased abundance of interstitial cells, which was found in 22% of the cases and often as soon as the second day, there were inflammatory phenomena and interstitial infiltrations which only appeared late and in slight degree. In the arteries (coronary, aorta, femoral, mesenteric) there were changes in the elastic coat in 2 cases, which could hardly be attributed, however, to toxin treatment lasting only 2 days. These results are in opposition to Wiesel's findings of injury of the elastic tissue of the media by diphtheria. The parenchymatous heart-muscle changes are to be regarded as the cause of death, and where they are lacking it is probably central paralyses.

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(1f—94)

**Pathologico-Anatomic Changes in the Peripheral Nervous System in Typhus. IV, V.**

*Morgenstern, Virchow's Arch. f. path. Anat., Berlin, 238:223, June 14, 1922.*

In 10 cases, the author found involvement of the peripheral nerves, including, in the order of frequency, the sciatic, ulnar, peroneal, median, cardiac, vagus and radial nerves. Histologically, there is a form of interstitial polyneuritis characteristic of typhus with peculiar nodule formation, which originates from the vessel endothelium and adventitia cells with involvement of the more resistant connective tissue cells. There is also a periaxillary neuritis which is distinguished from that in other infectious diseases by the fact that the fibers are pushed apart by the nodules. With longitudinally placed nodules only one nerve-fiber degenerates, with transverse nodules an entire bundle has the picture of Wallerian degeneration.

The pathologic changes in the nervous system in typhus are described as a gliogranulomatosis perivascularis polio-encephalitica exanthematica. The cadavers of 15 typhus patients who died without complications on the fifteenth or sixteenth days, at 20 to 25 years of age, were subjected to autopsy after 5 to 13 hours. Qualitatively the changes were always the same; they only varied quantitatively. The changes in the brain substance were (1) vasculitis with sharply defined fatty degeneration of the vessel wall; (2) varying degrees of degeneration and fatty infiltration of nerve-cells; (3) degenerative changes in the nerve-fibers with destruction of medullary sheaths and axis cylinders, and (4) reaction of the glia, partly in the form of nodules in definite relation to the vessels, partly in the form of diffuse changes with formation of giant glia cells and increase of satellite cells. The nodules were much more numerous in the gray substance than in the white. The author attributes the formation of the nodules to the action of the parasites themselves; the toxins on the other hand seem to produce the diffuse changes in the glia and in the nerve-cells and fibers. The author regards the nodule formation as a specific perivascular granulomatosis.

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**SECTION 1. ANATOMY, PHYSIOLOGY  
AND BACTERIOLOGY**

**1a. ANATOMY AND PHYSIOLOGY**

**ANATOMY, EMBRYOLOGY, HISTOLOGY**

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**The Synthetic Theory of the Animal Body Based on the Reproductive Capacity of the Tissue Systems of the Higher Orders.**

*Martin Heidenhain, Deutsch. med. Wchnschr., Leipzig, 48:1240, Sept. 15, 1922.*

The conventional analytic method of research in the field of morphology has not only left great gaps in our knowledge but has even led to serious errors. The author tries to demonstrate that by a change to the synthetic method of reasoning many old errors can be corrected and the foundations laid for a synthetic theory of the animal body. Schwann conceived of the tissue cells as organisms that were independent to a high degree and held that the life of the body as a whole was due to the sum of the activity of the individual cells. In this confusion of tissue cells and cell personalities lies a fundamental error of the analytic theory, which transforms the animal as well as the plant body into an aggregate of unicellular organisms. Later the cells were regarded simply as building stones of the organism, so that neither the cells nor the assimilating, growing and differentiating inter-cellular substances were assigned to their proper relation in the animal body.

Efforts to arrive at a decisive analytic theory of the animal body and to reduce the total structure of the body to form-constituents equal to one another, are justified.

If one changes to the synthetic theory, the cells represent a divisible system; all the living organ cells contained in the body, such as nuclei, chromosomes, centers and chlorophyl bodies, must have the same kind of capacity for reproduction. In the course of ontogenesis, numerous cell systems or tissue systems of a higher order are formed by true synthesis, become capable of reproduction by division and are, therefore, capable of producing numerous descendants of the same kind. The taste buds, the glands of the small intestine and villi, the acini and excretory ducts of the racemose glands, as well as all the tissue systems of the kidneys, belong to the tissue systems that are capable of division. The growth of the salivary gland as a whole is similar to that of the stalk of a polyp. The phenomena of division are developmental-physiologic analogues to the numerous processes of nonsexual reproduction in invertebrate animals. Here, too, the principle of biology that all living things come from living organisms, holds good.

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**The Anatomic Relations of the Sensory Nerve of the External Auditory Canal and of the Posterior Auricular Branch of the Facial.**

*A. Hovelacque and J. Rousset, Bull. et mém. Soc. anat. de Paris, 92: 318, July, 1922.*

The nerve branches designated in the title vary greatly. Seven dissections have been examined. Both nerves originate outside the petrous portion of the temporal bone, sometimes just below the stylo-mastoid foramen, sometimes 3 or 4 mm. from it. Exceptionally, the sensory branch distributed to the external auditory canal may be given off lower than the posterior auricular branch. Sometimes only 1 branch exists, or 3 nerves may occur, owing to the primary division into two of the posterior auricular.

Three principal types occur: (1) The classic relations exist, but the distribution of the posterior auricular is always quite extensive, supplying the mastoid and inferior parietal regions and often the posterior aspect of the aural pavillion. More rarely, the branch supplying the auditory canal may also innervate the deep aspect of the pavillion and mastoid region. The point at which this branch perforates the cartilage varies considerably, but it is usually situated at the lower border of the posterior auricular muscle. In this type, the posterior auricular branch is both sensory and motor. (2) The posterior auricular branch is purely sensory and is distributed as in Type 1. Before perforating the cartilage, the branch in the auditory canal supplies the 2 auricular muscles and sometimes the transverse muscles of the nucha. Cutaneous collaterals may occur, as in Type 1. (3) A single nerve occupies the tympanomastoid groove. In its superior portion, it leaves the anterior border of the mastoid, reaches the auricular muscles deeply, innervates them and perforates the wall of the auditory canal high up. Numerous anastomoses occur in the skin fibers, between both branches of the facial, with Arnold's great occipital nerve and with the auricular branch of the cervical plexus. The relations of the 2 latter anastomoses are very variable.

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**A Study of Agglomerular Kidneys.**

*J. Verne, Arch. d'anat. micr., Paris, 18: 357, Aug. 15, 1922.*

An agglomerular structure exists in the renal apparatus of lophobranchial fishes. Species examined by the author, occurring in the Mediterranean, Red Sea, and Channel, include *Syngnathus dumerilii*, *Syngnathus acus*, *Nerophis lumbriciformis*, *Entelurus anguineus*, *Hippocampus brevirostris*, and *Hippocampus guttulatus*. The fixative solutions of Bouin, Flemming, Regaud and Carnoy were employed. The stains were iron hematoxylin, the Benda stain, safranin and Altmann's eosin-methylene-blue. Frozen and unfixed sections were also examined.

The kidney of lophobranchial fishes consists of a mesonephros supplied purely by the portal vein. It is formed asymmetrically in a single mass, along a single, right cardinal vein. Both Wolff's canals persist, showing that there is no renal atrophy. A paired pronephros, accompanied by 2 glomeruli, exists for a short time precedent to the



asymmetrical mesonephros, which is thus secondary. Malpighian glomeruli are absent in the mesonephros, owing to the venous circulation and absence of arteries. The absence of glomeruli results in simplification of the urinary tubules, of which only the secretory portion and entrance into the ureter exist. The entire urine is excreted by the tubules, a function shared by tubules and glomeruli where the latter occur, and the urinary secretion is less active than in animals supplied with glomeruli. Certain substances, such as methylene-blue and caffein, are not eliminated by the aglomerular kidney, as they are by the glomerular structure, but by the tubules and peritoneal endothelium.

The urinary tubule includes 2 segments, composed of similar cells having an intensely active secretory function, as indicated by their nucleus and chondriome. The cells of 1 segment are ciliated, those of the other not. The chondriome is polymorphous, presenting mitochondria and small rods. Renal structure depends on the blood supply, the absence of glomeruli and the simple tubular structure being due to the lack of renal arteries. In vertebrates, the essential element of urinary secretion is not the glomerulus, but the renal epithelium. However, the glomerulus shares in secretion in animals in which it exists. Physiologically and anatomically, kidneys should be distinguished as those of venous and those of arterial circulation. The venous circulation is slow and the blood rich in  $\text{CO}_2$ . Conditions in the tubules of aglomerular are not the same as in the tubules of glomerular kidneys. Lymphoid tissue is abundant in the kidneys of lophobranchial fishes, absent in mammals. Between these extremes there are many gradations. Aglomerular kidneys illustrate the secretion of urine by the cells of the tubules and thus support the Bowman-Heidenhain theory that urine is formed by true secretion and not by mere absorption from the blood. The secretion appears to be as active by nonciliated, as by ciliated, cells. Urea produces diuresis by direct action upon the renal cells, while caffein acts upon the circulation and increases urinary excretion secondarily. The histology is shown by excellent plates.

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**On the Permeability to Dyestuffs of the Placenta of the Albino Rat and the White Mouse.**

*Yoshitaka Shimidzu, Am. J. Physiol., 62:202, Oct. 1, 1922.*

The author investigated the permeability of the placenta for a number of dyestuffs, hoping to get some information about the passage of colloidal material through the placenta. As experimental animals the pregnant albino rat and white mouse at or near full term were used. The solution of each dye was usually injected hypodermically between the scapulas. At varying intervals from 5 to 48 hours after the injection, the fetuses were removed by cesarean section and the coloration of the mother and fetuses was determined. All placentas were thoroughly examined for pathologic changes and if any abnormality was found the animal was eliminated from the series. The author used only those dyes which are easily soluble in water or in physiologic salt solution and which stain the living animal without any serious ill effects. Of the 23 dyes used, 16 penetrated the placenta

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after their injection into pregnant animals, while the other 7 were not found in the fetal body. The placenta was found to be permeable to alizarin-SO<sub>3</sub>Na, Biebrich's scarlet, Bismarck brown, Bordeaux red, dahlia, eosin w. s., fuchsin (acid), indigo carmin, light green F S, methylviolet 6B, methylene blue, neutral red, Nile blue, orange G, safranin and toluidin blue, and nonpermeable to alkali blue, anilin blue w. s., Congo red, isamin blue, lithium carmin, Niagara blue 2B and trypan blue. The placenta was permeable to all of the basic dyes. Among the 15 acid dyes 8 penetrated the placenta, while 7 could not be found in the fetus. The permeability of the placenta for dyes the author found to be entirely similar in the albino rat and mouse. The power of the dyes to pass through the placenta appears to run parallel to the colloidal state of their solution in the serum, especially to their ability to spread in a gel of high percentage. So far as its permeability for dyes is concerned the placenta acts as an ultrafilter, and in view of the size of the colloidal particles which can pass the placenta the author infers that proteins must be decomposed into their components in order to pass from the mother to the fetus.

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**Changes in the Mammary Gland of the Albino Rat (*Mus Norvegicus Albinus*) during Lactation and Involution.**

*Le Roy M. A. Maeder, Am. J. Anat., 31: 1, Sept. 15, 1922.*

In this investigation the author used 28 primiparous and 3 virgin albino rats. The animals were killed by ether and immediately weighed and measured. The mammary glands with their attached skin were removed intact. The stages in lactation were used for cleared total mounts as well as for histologic preparations. A modification of the method employed by Myers was found to be more suitable for the gland at this stage. The whole integument after removal was placed flat upon a cork sheet and held in position with the glandular surface up. The whole preparation was then fixed in Zenker's solution for 24 hours, washed for 24 hours in running water, and then carried up through the various grades of alcohol to 80%. Appropriate pieces for histologic sections were removed from selected areas. At this point the specimen for the final cleared preparation (total mount) was secured. Starting at one edge, the tela subcutanea was split from the corium, and this process continued over the entire area of the integument, using a sharp safety-razor blade for the purpose. The very thin fascial envelope containing the glandular tissue which was thus obtained was dehydrated, carried through xylol into beechwood creosote, mounted upon a glass frame, placed in a thin specimen jar of appropriate size and covered with beechwood creosote. Staining was found to be unnecessary, for after several weeks in beechwood creosote the darker glandular tissue could be seen in bold relief against the relatively transparent fascial envelope.

In recently killed lactating animals the mammary glands were seen to be well-defined masses elevated above the surface of the rest of the skin. The nipple was long and prominent. In the stages of involution, after 2 weeks, the glands were much smaller and less clearly defined. Cleared preparations (total mounts) of the glands in lactation

showed that the macroscopic aspect of the gland remained unchanged throughout lactation and was the same as at the end of pregnancy. Concerning the histology during lactation the author remarks that in general any stage of the series of glands in lactation may be taken to represent the characteristic appearance of the gland during this period and at the end of pregnancy. It was found that the macroscopic and microscopic structures of the mammary gland remained practically unchanged throughout the period of lactation in the albino rat. Involution is first evidenced by the occurrence, in the acinar epithelium, of larger fat-droplets which crowd the nuclei and deform them; also by a decrease in the size of the alveoli and a loss of the contents in their lumina. Apparently during involution the contents of the lumina and ducts are removed by simple absorption. There is nothing to indicate that in the rat leukocytes have anything to do with the removal of the secretion.

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**A Human Ovarian Graft Surviving for Four Months within the Peritoneal Cavity of a Rabbit.**

*Mauclaire and Lachowsky, Bull. et mém. Soc. anat. de Paris, 92: 338, July, 1922.*

The 2 halves of an ovary removed from an insane patient were grafted into the peritoneal cavities of 2 rabbits. The animals were killed and examined 4 months later. The grafts, surrounded by mesentery which appeared to have nourished them, were not more than half diminished in size. Histologic examination showed fibrous corpora lutea, and irregular groups of interstitial cells. The cells must have been persistent or had developed after grafting. In either case, the receiving animal tissues had had some effect upon the graft.

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**The Significance of the Prechordal Plate: An Interpretative Study.**

*Howard B. Adelman, Am. J. Anat., 31: 55, Sept. 15, 1922.*

In this paper the term "prechordal plate" is used to designate the diffuse mass of tissue in which the notochord ends anteriorly. By means of a detailed description and numerous figures the author shows that this structure arises in both the chick and the shark in a region which is morphologically the equivalent of the primitive dorsal or cranial lip of the blastopore. In both of these forms the prechordal plate maintains its primitive preaxial position due to the fact that the axial portion of the body is formed posterior to it out of the lips of the blastopore or an homologous structure. The prechordal plate is a structure which is essentially mesodermal in its potentialities, in the chick giving rise to mesoderm in the anterior region of the head, and in the shark forming certain of the so-called head somites together with a quantity of head mesenchyme. In neither chick nor shark does the prechordal plate give rise to notochordal material, but it maintains a relatively constant size until it begins its differentiation into mesenchyme or head somites, or

both, as the case may be. The prechordal plate is therefore to be considered as preaxial mesoderm, which is observed to be continuous posteriorly with the paraxial mesoderm. The undifferentiated mass of material anterior to the notochord may account for certain types of tumors found frequently in the region of the hypophysis, as, for instance, epignathus.

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**The Growth of the Skull under Physiologic and Pathologic Conditions.**

*Hedda Weinnoldt, Beitr. z. path. Anat. etc., Jena, 70:345, Aug. 26, 1922.*

Premature synostosis of the sutures has an influence on the form of the skull, as it has an inhibitory action on the interstitial increase in surface demonstrated by Thoma. The inhibition of interstitial growth of surface acts particularly in the direction perpendicular to the ossified suture, while there is an increased surface growth parallel to it. Ordinarily there is not a permanent increase of pressure in such a skull because the nonsynostotic parts of the skull undergo compensatory enlargement. In spite of this, however, such synostotic skulls must furnish a point of least resistance in the body, for they seem to be especially predisposed to certain diseases. According to the author's material, tuberculous meningitis is one of the most frequent causes of death in cases with premature synostosis. Also intercurrent rises of pressure cause death oftener than under normal conditions. The cause of premature synostosis, aside from disturbances in the germ anlage, is almost exclusively trauma. After birth there is the acute trauma that the child often suffers in his early years while learning to walk. Also chronic intra-uterine trauma of the sutures plays a great part. The lateral compression which in mild degrees leads to uncomplicated dolichocephaly, when it becomes stronger pushes the sutures into or over one another, and the chronic irritation leads to synostosis.

These pathologic dolichocephalies are clearly distinguished from the physiologic ones, so that the one cannot be regarded simply as a greater degree of development of the other. There is no proof so far of acute trauma; it is only a hypothesis. The author believes that her autopsy protocols and findings which are illustrated by numerous pictures, prove that as a matter of fact suture trauma does occur much more frequently than has been believed. In physiologic suture synostosis, the musculature of the skull, aside from intracranial pressure, is the chief factor which causes the sutures to remain open. The lack of either one of these 2 factors leads to ossification of the sutures, which can, therefore, be designated as physiologic only conditionally. The synostosis of the frontal suture is not to be explained in the same way. Here the changed laws of gravitation after birth, especially the action of the facial part of the skull, play a part.

In the theory of the development of the form of the skull, the author agrees on the whole with Thoma. Only she cannot agree with his pressure pole theory. In the early fetal skull, the intracranial pressure is almost uniform throughout. There are no local rises of pressure. Therefore the author does not recognize the purely histomechanical explanation of the origin of the ossification centers. On the

contrary, she holds fast to the explanation that the first anlage of tissues and organs comes about by inherited characteristics of the organism. Only later do mechanical factors begin to assert their influence.

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**The Effect of Pressure and Relaxation of Pressure on Bone Growth in the Skull.**

*H. Loeschcke and Hedda Weinnoldt, Beitr. z. path. Anat. etc., Jena, 70:406, Aug. 26, 1922.*

The authors first made histologic examinations of a series of normal skulls of different ages in order to test the influence of brain growth on the skull. They found that the growing brain exercises a constant pressure on the skull which leads to progressive absorption of the internal table. In the intervals of growth some parallel lamellas may again be deposited on the internal table, which, however, with progressive growth of the brain and skull again undergo absorption. The thickness of the skull is restored by apposition on the external table, the marrow spaces are filled up by tertiary bone tissue from the spongiosa and are continually reformed in the external younger bone layers by processes of absorption. Between the twentieth and thirtieth years the growth of the skull and brain comes to a standstill, but the time is subject to great individual variations. At this stage the histologic picture shows internally and externally narrow borders of parallel lamellas which are interspersed with tertiary lamellas along the vessels, as a sign of their maturity. Interruptions of lamellas are only rarely found. While the digital impressions at the vertex of the skull almost completely disappear, they are as well formed as before on the lateral parts and at the base and show pronounced pictures of absorption.

In the stage of senile decrease of volume there is active apposition of parallel lamellas on the internal table, while the digital impressions at the vertex have completely disappeared. The bone apposition is limited exclusively to the roof of the skull while at the base further absorption is to be observed. In a series of cases the authors found in the roentgenogram that the absorption and dissolution of the original corticalis interna had not been completed in spite of pronounced lamellar apposition on the internal table, and that a zone of condensation corresponding to the original corticalis could then be demonstrated in the diploë of the new-formed bone. The external table after the end of apposition growth in youth showed pronounced signs of absorption in all cases in which bone was apposed on the interna. But apposition on the inner side and absorption on the outer side do not always take place with equal rapidity. In bones with pronounced osteoporosis, the signs of absorption prevail. The skull can again assume forms which are similar to those of the young skull. The space in the skull is then equalized by an increase in the cerebrospinal fluid. The authors think that the cyanotic hyperostoses of Thoma are the result of a preliminary cachectic decrease of volume of the brain and they consider them parallel with the senile vacuum proliferations of the internal table. The thickening of the skull in pregnancy may be partly due to decrease in volume of the brain, partly, in analogy with other bone proliferations in pregnancy, due to a normal stimulus.



The authors showed in numerous preparations from children in the first years of life that the brain as it increases in weight sinks down in the skull and causes pressure atrophy at places where it rests, and in the opposite ones that have been relieved from pressure, proliferations, as in the frontal parts there was marked apposition and in the occipital parts great thinning of the bone, corresponding to the predominant position of the children. Wieland's congenital lacunar skull is also attributed by the authors to atrophy as a result of pressure injury by the brain. As to the behavior of the skull in pathologically increased pressure, it is found that the stronger the internal pressure the stronger the pressure atrophy of the internal table, which is manifested first by more pronounced and deeper digital impressions, and on higher pressure by an increasing roughness of the inner surface of the skull which resembles a grater, and occasionally on rapid absorption from the inner surface it may lead to opening of the marrow spaces. The external table in youthful cases with great absorption from the internal table shows a strikingly strong apposition of parallel lamellas, that is, the sign of increased growth.

The authors think that the reasons why the 2 tables mutually affect each other are static in nature. Here not only are the pressure and the mass of the compressed material to be taken into consideration, but also the quality of the material. In bone, both the gelatin and the calcium content undergo great variations. Rachitic and osteoporotic bone is much less resistant to pressure than normal bone, and, therefore, it is much more rapidly broken down by pressure (lacunar skull in rickets and craniotabes). If a static balance is to be attained, it requires a considerably greater thickness of material, which as a matter of fact is found in the skulls of rachitic children. In answer to the question of why compressed bone atrophies and why bone relieved of pressure shows proliferation, the authors say that they think it is due to nutritive processes.

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### **Mammalian Hair and Tactile Spots.**

*Friedrich Maurer, Anat. Anz., Jena, 56:71, Sept. 5, 1922.*

There are 3 theories as to the histogenetic derivation of the mammalian hair: (1) The hairs are *orga. sui generis* and do not have any predecessors in the lower vertebrates. (2) The hairs have developed like the feathers of birds from the scales of the skin of lower animals, especially the reptiles. (3) The hairs of mammals have their predecessors in other epidermoid organs of lower vertebrates. Such organs are the skin sense organs of animal forms which live in the water; these have an important rôle but atrophy on the transition to life on land. The protective apparatus is the foundation for many organs which develop later in different ways. Uhlmann and Plate think that the tactile spots on the body scales and on the head are the precursors of mammalian hair. The author denies this theory. The tactile spots as well as the skin sense organs of water vertebrates are only topographically related to the scales. They are in no way organs of the reptilian scales, but skin sense organs. The finer relation of the nerves to the different forms of sense cells remains to be cleared up. In the skin sense organs of vertebrates living in water a specific sense nerve passes

from the papilla to the inner sense cells of the end bulb and forms a terminal network around the cells. In the tactile corpuscles of vertebrates living in the air, sense cells have been distinguished which are specially developed cylindric cells of the basal epidermis layer. The relation of the sensory skin nerves is not yet clear.

As to the histogenesis of the mammalian hair, the author takes as a starting point the development and structure of the individual hair with its follicle. We cannot speak of a primitive hair showing an ascending development; there are modifications only in the volume of one or the other part, the hair-shaft, the cortex, the medulla and epidermis; the connective tissue hair-follicle sheath; and the hair papilla. The follicle parts are always the same, and the root sheath always passes continuously into the adjoining epidermis, while the hair sheath, connected with the epidermis, grows out with the hair, but does not continue on the free shaft and stops with a free edge in the follicle. The hair-follicle sheaths are always the same and show an internal layer of circular fibers and an external one made up of bundles of longitudinal fibrils. The papilla contains the capillary network in connective tissue but has no sensory nerves. Hair is, therefore, a purely epidermoidal structure that uses the cutis only for fixation and nutrition. On the other hand, scales and feathers originate in the papillas of the cutis. The nerves which supply the hair are sensory skin nerves which enter the hair-follicle sheaths and the root sheaths from the side but do not pass through the papilla to the hair. In the tactile organ of Calotes, which is the species of agamid taken by Uhlmann-Preiss for study, it is incomprehensible why after the atrophy of the tactile cells, the horn cells above them should be preserved; for the organ does not sink into the deep tissues and does not form a follicle. The peg of horn on the sense cells acts on these by lever movements but they do not constitute supporting cells. If the tactile cells with the papilla nerves are destroyed on the development of a hair, the peg of horn has no further existence. From the picture of this tactile organ, it is impossible to recognize the origin of the hair sheath which is so characteristic of the mammalian hair.

It may be urged against the author's opinion that the hairs are horn organs, but not skin sense organs of vertebrates that live in the water. But the process of cornification can often be found in these forms too; the epidermis of the amphibia forms a stratum corneum, in which the skin-sense organs, especially the surrounding supporting cells, are found. This process of cornification can be increased, especially by the entrance of sensory skin nerves from outside. That the hairs extend over the whole body and the skin sense organs in amphibia are limited to some longitudinal lines along nerves, does not argue against the thesis of the author, who has never regarded the amphibia living today as the predecessors of a higher group of vertebrates. Credner described the group of Stegocephala, extraordinarily rich in forms, from which Sauropsida developed on the one hand and the present amphibia and mammals on the other. The former (Sauropsida) form uric acid on metabolism, the two latter excrete it. The morphologic relations are such that mammals are nearer to amphibia than to reptiles, even to the especially developed Calotes forms which stand somewhat aloof. Shedding of hair is explained by adaptation like moulting of birds, as a shedding of the skin does not occur as in reptiles. The latter, like the amphibia, cast off the stratum corneum through external influences.

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**Phylogenetic Origin of Milk Glands and Hair.**

*L. Plate, Anat. Anz., Jena, 56:65, Sept. 5, 1922.*

According to the opinion of Broman, the milk glands of mammals are analogous to the lateral organs of amphibia and fish. But the hair follicle cannot be regarded as a horn-producing gland. Glands are only those cells or cell complexes which discharge their secretion or excretion externally or internally but do not remain in constant connection with it. The hair follicle holds the hair fast as long as the latter is alive, but this does not make it a gland. According to Maurer, the hairs of mammals originate from the sense cells of the lateral sense buds. In these organs there are gland cells which become gland cells of the milk organ. In the first anlage of the milk gland, hairs are frequently to be found. These 3 points, as well as the serial arrangement of the milk glands and the appearance of the hair of mammals and the back glands of crocodiles on the same parts of the body as are preferred by the lateral sense buds, are said to support Broman's theory. They do not, however, harmonize with it. As the amphibia come to live on the land, the sense buds degenerate with hornification of the supporting and covering cells, but a column of horn projecting outward like a hair is never formed.

The sense buds lying back of the head are supplied from the lateral branch of the vagus, while the hairs are innervated by the spinal nerves; also the hairs cover the whole body uniformly with the exception of a few places, while the sense organs are connected with definite longitudinal lines. The Preiss-Uhlmann hypothesis is a much more plausible one. In the agamids, on most of the scales there are extremely small tactile hairs, which are regarded as preliminary stages of mammalian hair. The matrix cells of the epidermis are transformed into sense cells which are located on a small corium papilla provided with blood-vessels and nerves and above which a hair of horny cells extends. The pressure on this hair is transmitted to the sense cells which are surrounded by supporting cells: the tactile hair which is located in a follicle-like pocket in the epidermis presumably originates from the hornification of these 2 kinds of cells. Originally the mammalian hair had no medulla, which is still true of the tip of most hairs. In exfoliation, the old hair was pushed forward by the new and the 2 lay over one another. The tactile hairs probably enlarged and then pushed from the edge of the scale into the soft skin between 2 scales and grew inward, anchoring themselves firmly in the skin. Then they were abundantly innervated by the sensory nerves and the cells at the floor of the follicle became the producers of the horny masses of the hair.

Broman's theory that the gland cells of the lateral organs developed either into milk glands or tactile hairs is not tenable, because the sense buds of the amphibia do not have gland cells. In some fishes, sense buds have migrated into the subepithelial canals. The gland cells contained in these fill the canal with mucus, but it does not cornify. The frequent formation of hairs by the anlagen of milk glands is explained by the fact that milk glands are greatly enlarged sweat glands and these often enter the hair follicle. It is true that some urodeles have 3 lateral lines, a dorsal, a middle and a ventral one, extending over the entire body; but because they occupy the same parts of the body, organs of completely different construction, such as the glandless sense buds of the amphibia,

milk glands and hairs cannot be held to be homologous. According to the author's theory, the alveolar glands of the amphibia provided with epitheliogenetic musculature, by growing into the deep tissues became tubular glands for the purpose of making the scales glide more easily. After retrogression of the scales, mammalian hairs developed from these very fine hairs and entered into relation with these glands which were transformed into sweat glands.

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### **Celluloid in Microtechnic.**

*Oreste Nuzzi, Riforma med., Naples, 38:818, Aug. 28, 1922.*

The author, in order to avoid the inconveniences caused by the ordinary cover glass (its fragility, dimensions, high cost) in the course of some histologic experiments, has used celluloid membrane. The experiment was very satisfactory, fulfilling all the conditions of a satisfactory technic. It is possible to use the ordinary cinematograph or photographic films that have already been used, by simply removing the layer of gelatin. The index of refraction of celluloid (1.5002) is near enough to that of cedar oil used for immersion (1.5100). Best results are obtained with celluloid not thicker than 0.11 mm., which is markedly less than the thickness of the ordinary cover-glass (0.14-0.17). Considering the importance of the thickness of the cover-glass in relation to the clearness of the image, this does not offer any disadvantage, either when used with a weak dry objective, or with the strong objective with immersion. Considering the homogeneity of the medium, the clearness of the image is almost, in fact, independent of the thickness of the cover-glass; even with dry objectives of higher power (8 of the Koriska) the clearness of the image is sufficient for ordinary observations; to get the best image, recourse may be had to the corrective objective.

The sheet of celluloid may be cut easily with ordinary scissors, and in any form desired; in enclosing the preparations in Canada balsam or any other medium, no difficulty is encountered, because the flexibility of the membrane permits complete expulsion of the air. The celluloid is washed with tepid water, to which a little potassa has been added, rinsed in ordinary water, then in distilled water, and dried at room temperature, with protection from dust. The membrane is, of course, ruined by fire, acetone, amyl acetate or by an ether-alcohol mixture. The utility of celluloid, well recognized for ordinary preparations, is even greater for sections in series and for large sections of internal organs, of embryos, fetuses, etc. The author is convinced that by employing celluloid also as a substitute for the slide, it is possible to obtain preparations superior to those that are had by the method of Giacomini and that of Rupp.

The idea of using celluloid had already occurred to others who, however, complained that a short time after making the preparation, the celluloid warped so that the Canada balsam would not fix it to the glass. According to the author, this resulted from the too great thickness of the celluloid (0.2-0.4 mm.) employed, making it too stiff. He has employed preparations made by a special means by which the celluloid is perfectly adherent and acts absolutely like the ordinary glass.

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**Elements Resembling Interstitial Cells in the Epididymis.**

*J. Kyrle, Beitr. z. path. Anat. etc., Jena, 70:520, Aug. 26, 1922.*

In a section through the head of the epididymis of a dog whose vas deferens had been ligated, the author found, around tubules that were to be regarded as efferent ducts, cell complexes in the connective tissue which at first glance appeared to be Leydig's cells. Similar cells were found in specimens from 2 dogs whose testicles and epididymes had been injured by x-rays. In 2 further specimens were demonstrated these peculiar cells which are sometimes found in the epididymides of dogs. A search for similar structures in human testicles disclosed in the epididymis of an abnormally atrophied testicle accumulations of interstitial cells of tumor-like appearance morphologically identical with Leydig's cells. Similar cells occurred in another epididymis, in which case the testicle had been injured. It requires further investigation to determine whether these peculiar elements resembling Leydig's cells must be reckoned with in the epididymis, and whether they have a special functional significance.

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**Elastin "H".**

*O. Ewald, Münch. med. Wchnschr., 69:1218, Aug. 18, 1922.*

Dr. Hollborn of Leipsic has recently devised a new stain for showing elastic fibers in tissues: It is an amphochromatic stain which, dissolved in nitric acid and alcohol, colors the elastic fibers red to brown-red and the rest of the tissue blue. Conservation and embedding have no special effect on the action of the stain. Of the stain, 0.5 gm. is dissolved in 50 c.c. 70% alcohol and 1 c.c. pure nitric acid with moderate heating in a water-bath. The stain can be used immediately after filtration. The sections are left 6-10 hours in the solution and then passed through 96% alcohol, absolute alcohol and xylol into balsam. The stain can also be used for tuberculous sputums to show the elastic fibers.

**ABNORMITIES**

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**The Histology of a Testis from a Case of Human Hermaphroditism, with a Consideration of the Significance of Hermaphroditism in Relation to the Question of Sex Differentiation.**

*H. E. Jordan, Am. J. Anat., 31:27, Sept. 15, 1922.*

The author discusses the histology of a testicle removed from the groin of a married woman who was one of a family of hermaphrodites. In the microscopic picture 2 elements predominated: remnants of seminal tubules and masses of interstitial cells. The fibrous stroma was relatively scanty. The seminal tubules, considerably smaller than normal, showed a thickened, hyalinized wall, containing a few scattered and shriveled nuclei. The interstitial cells occurred in masses of varying size among the disappearing tubules. The interstitial cells varied in shape and were observed to contain a large or small vesicular nucleus



or a chromatic nucleus. The globus major proper, with its ductuli efferentes, was found to be approximately normal. Lateral and cephalad to the caput, however, there occurred a spheroidal mass of smooth-muscle tissue, containing relatively little connective tissue and only few blood-vessels. The nodule is of especial interest because it is approximately in the position of a nodule described in connection with a similar testis of similar hermaphrodites both by Gudernatsch and by Whitehead. The ductus epididymitis in certain portions appeared practically normal, both as concerns the connective-tissue portion of the wall and the lining epithelium. The ductus deferens appeared approximately normal, except toward the end where it became constricted and fused with the caput epididymidis. The preservation of the testis rendered it unfavorable for detailed cytologic study. It was impossible to determine whether the greatly vacuolated condition of some of the interstitial cells should be interpreted as degeneration changes or the result of a solution of certain lipid elements.

The undisputed occurrence of both ovaries and testicles in the same individual in 3 recorded cases shows that true anatomic hermaphroditism is possible in man as well as in other animals. Such instances admit theoretically, the author says, of 1 of 3 explanations: (1) The human embryo is originally potentially hermaphroditic, and the definitive sex of an individual results from the inhibition and later suppression of the opposite sex primordium, or, as in the case of true hermaphroditism, an approximately equal development of both primordia following a relatively balanced condition of both sex potencies. In other words, hermaphroditism in man represents a reversion to an earlier ancestral condition and signifies the adult persistence and expression of a normal embryonic potentiality. (2) True glandular hermaphroditism is the result of an atypical fertilization, possibly the penetration of an egg by an abnormal sperm (e.g. one with the unreduced number of chromosomes) or by both a male and a female determining sperm. (3) The zygotically determined sex, following fertilization by either a male or a female determining sperm, is subsequently rendered potentially bisexual through some unusual contingency during development, either through the action of an opposite sex hormone or the inclusion of a portion of another embryo.

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### **Congenital Defects from the Standpoint of the Fetalization Theory.**

*L. Bolk, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:1536, Sept. 30, 1922.*

Certain defects due to arrested development, such as coloboma, harelip, cleft palate, hypospadia, are not incompatible with normal life. Others, such as acardia, anencephalia, make life impossible. Arrested development is due to quantitative modifications of the factor governing the morphology of the body as a whole. In many respects the development of the human body is more primitive than that of the apes. Certain structures that continue to full development in the apes are arrested in man. The factor governing bodily form is endogenous. Somatically, man represents the mature fetal stage of the primates. The human form results from a "fetalization" process, which is directed by the

endogenous factor. The latter is an endocrine influence. Endocrine hormones regulate mammalian metabolism and morphology, the latter function being secondary, the former primary. Hormones stimulate and inhibit. Development occurs at a slower tempo in man than in other primates. On account of differences in the tempo, a character developed in one race may be suppressed in another. Owing to this principle, the white races are higher than the black, and of the former, the Nordic type represents the highest human variation because it is most actively fetalized. According to the same principle, man is superior to woman. The human form is essentially fetal.

Human morphologic and histologic differentiation is checked by inhibitory endocrine secretions. The straight or convex nose of the white races represents full development, the concave nose, occurring in colored races and as an infantile character in the white, is fetal. The straight nose results from endocrine stimulation. The principle may be concerned in the production of mongolian idiocy. The fetalization theory and principle are inclusive and are based on unity of causation and mechanism.

Once present, a defect may modify the entire development, or quantitative endocrine effects may produce abnormal inhibition. The fetalization theory illuminates teratology. Variation of species depends on qualitative effects. The increased inhibition that produces morphologic variations in the same species is quantitative.

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**Anomalies of the Sphenopalatine Ganglion, Otic Ganglion and Nerve of the Tensor Veli Palati.**

*Jean Rousset, Bull. et mém. Soc. anat. de Paris, 92: 333, July, 1922.*

In this specimen, the right sphenopalatine ganglion was triangular, unusually large and adherent to the maxillary nerve. Bock's pharyngeal nerve arose from the apex by 2 roots. The vidian nerve was given off more externally. An anterior and posterior branch, seemingly of the palatine nerve, were given off below. The anterior trunk consisted of the anterior and middle palatine nerves, and the posterior trunk of the 2 large posterior palatine nerves. The anterior palatine nerve received a dichotomous branch. A trunk as large as that of the superior maxillary arose from the upper pole of the ganglion, forming 2 secondary branches. The anterior and internal formed some 6 subordinate branches. The posterior and external united with the Gasserian ganglion. No fibers were distributed to the Gasserian ganglion on the opposite side. In another dissection, a ganglion not identical with, but replacing, the otic ganglion, was attached by a pedicle to the left inferior maxillary nerve, just below the foramen ovale. Opposite the pedicle, a trunk supplied fibers to the parotid region. Another trunk extended to the sympathetic plexus about the external carotid artery. Below the pedicle, a branch was directed to the mastoid periosteum and skin of the parotid region. It anastomosed with the ganglion in 2 groups of fibers. At the level of the foramen ovale, a nerve arose, by 3 branches, from the internal aspect of the inferior maxillary. This nerve supplied a branch to the venous plexus about the foramen ovale and expanded in an anastomosis with the chorda tympani. Internally from the trunk of

the inferior maxillary, a small expansion gave off an anterior and posterior branch. The facial trunk was unusually thin.

In 1 subject, a superior and inferior hiatus were present in the pterygoid tendon of the internal pterygoid muscle. The nerve supplying the tensor veli palati, after leaving the common trunk distributed to the internal pterygoid muscle, entered the posterior border of the latter, passed into its tendon, crossed the upper hiatus, issued through the lower hiatus and entered the external aspect of the tensor veli. In another case, the pterygoid origin of the internal pterygoid muscle was continued upon the internal lip of the foramen ovale and spine of the sphenoid, extending to the base of the styloid process. A thin and flat tendon arose from this origin, becoming denser to form a stronger tendon bearing fleshy fibers lost in the upper third of the internal pterygoid muscle. This tendon concealed the inferior maxillary nerve. The nerve supplying the internal pterygoid was applied on the external aspect of the tendon, perforating it at the point of origin of the fleshy fibers. The nerve supplying the tensor veli palati perforated the tendon at the base of the internal wing of the sphenoid. Civinini's ligament was ossified.

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**The Pathogenesis of True Transposition of the Arteries of the Base of the Heart.**

*P. Hickel, Bull. et mém. Soc. anat. de Paris, 92:294, July, 1922.*

Two unusual cardiac conditions are reported: (1) The left auricle received the pulmonary veins. A patent foramen ovale allowed blood to enter from the right auricle, but the blood did not pass in the opposite direction. There was no interventricular communication. The pulmonary artery was given off from the left ventricle, the aorta from the right. The left coronary artery opened into the left sinus; the right, into the posterior sinus, the right sinus having no orifice. Cyanosis was the only symptom present; the venous, peripheral circulation could not be sufficiently aerated. (2) The right ventricle was enlarged and gave rise to the aorta. The pulmonary artery arose from the left ventricle. The foramen ovale was slightly patent. There was an interventricular communication. The coronaries were situated as in Case 1. The pulmonary artery was constricted. The facts show that the abnormal position of the bulbar septum is not due to Rokitansky's supposed abnormal insertion, but to incomplete torsion, the interventricular septum not being concerned. The incomplete torsion is shown by the relations of the pulmonary artery, aorta and coronaries. The septal torsion is due to the torsion produced by the 2 primitive arterial currents. The interventricular septum closes before the auricular. The blood current continues spirally within the auricle and, if it be abnormal, the septum will be turned incompletely.

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**An Anomaly of the Subrenal Segment of the Inferior Vena Cava.**

*Pierre Wertheimer, Bull. et mém. Soc. anat. de Paris, 92:316, July, 1922.*

In this specimen, the 2 iliac veins united in front of the body of the fifth lumbar vertebra, behind the left common iliac artery and below

and to the left of the aortic branching. The inferior vena cava was thus to the left of the aorta. It was situated on the anterolateral aspect of the vertebral column as far as the disk between the second and third lumbar vertebrae. Directed thence obliquely above and to the right, it passed in front of the aorta in the angle between the aorta and superior mesenteric artery. Crossing the right renal artery, the inferior vena cava resumed its normal position above the kidney. This anomaly belongs in Augier's fifth class. It is due to persistence of the normally atrophying left cardinal vein. The cause has not been determined. The anomaly described accompanies later development occurring in the venous system.

## ARTIFICIAL TISSUE CULTURES

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### **A Pure Strain of Cartilage Cells in Vitro.**

*Albert Fischer, J. Exper. Med., 36: 379, Oct. 1, 1922.*

In the eye of the chick embryo was found an anatomic locus electus for obtaining pure cartilage free from any other tissue elements. With this material it was possible to obtain pure cultures of cartilage cells. The culture medium was the same as that generally used for connective-tissue cells and epithelium, consisting of equal parts of adult chicken plasma and juice from chick embryos. The fragments of cartilage were placed on the surface of the coagulated plasma medium. Usually the growth did not begin in a promising way, but after 3-5 passages it became very active. When an attempt was made to transfer such a piece of cartilage into a new medium, after it had been embedded in the coagulum for 2 or 3 days, it proved impossible. An attempt was then made to place one of the small pieces of cartilage on the free surface of the clotted medium. As soon as this was done, the cells began migrating and progressively became more active and formed huge cultures. These new cells grew in some ways like epithelium, forming thin, delicate membranes, while the individual cells were in close contact. These cultures could readily be transferred to a fresh medium.

When first examined, it seemed as if a new kind of tissue had formed. The amorphous hyaline substance had disappeared and the cartilage cells grew and proliferated very actively side by side, without forming any of the hyaline substance. The cells were about the size of small lymphocytes and the resemblance was rather striking. From the surface-cultivated cartilage, the same process of breaking down of the hyaline substance took place and a different type of cells migrated. All the transition forms could be studied here, from the small lymphocyte-like cartilage cell to the much larger cell which finally characterized the active cartilage cultures. If, in this stage, the culture is transferred to the middle of the coagulum, it grows well and does not revert to the small type cells. The strain of cartilage cells now under cultivation is more than 3 months old, grows very actively, and can be made to multiply. Of all tissues hitherto cultivated in vitro, it resembles epithelium most, because of its characteristic growth in membranes. The cartilage liquefies the medium much more than epithelium and connective-tissue cells do.

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**Cultures of Organized Tissues.**

*Albert Fischer, J. Exper. Med., 36:393, Oct. 1, 1922.*

An artificial organism, composed of a complex of tissues, was cultivated for a long period of time. Small fragments of intestine of chick embryos 20-21 days old were placed in a suitable medium. The epithelium proliferated and completely covered the fragment of intestine after 4-6 days. A small body was thus formed, round or oblong in shape, surrounded by cylindric epithelium and containing epithelial, connective, and muscle tissues, endothelium, and ameboid cells. After a month's cultivation in vitro, no necrosis had occurred. Therefore, it may be assumed that, through the intestinal epithelium, the medium supplied the intestinal tissue with sufficient nourishment. No uncontrolled proliferation took place after the epithelium had covered and surrounded the entire fragment. The cultivation of complex tissues will facilitate the study of interactions of the different cells under various conditions. In some experiments, pure cultures of epithelial cells were grafted into such an organism without difficulty. The growth of malignant cells could be studied in the same way. When the organism was placed in a fluid medium, the epithelium remained normal but the stroma disappeared. It seems that plasma played an important rôle in the maintenance of the tissues in their normal condition.

**GENERAL PHYSIOLOGY**

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**The Excitatory State.**

*W. M. Bayliss, Bull. Johns Hopkins Hosp., 33:347, Oct., 1922.*

It has been shown that changes in consistency may be indicative of activity, as when a sol becomes a jelly by electric stimulation of protoplasm. Nerve and muscle have been regarded as the excitable tissues par excellence, due to the fact that their response is rapid and obvious; however, all living tissues are excitable in that they respond by change of some sort to external influences. There are 2 aspects of muscular contraction in connection with the problem of interfaces. The first of these concerns the mode of production of the state of tension. The work of A. V. Hill has shown that the magnitude of a contraction depends on the length of the fibers when the contraction begins, and the controlling factor is one of surface, not of volume. His conclusions are confirmed by the author's experiments made to determine the temperature coefficient of the contractile stress. This is negative, the more powerful contraction being at the lower temperature. A surface tension phenomenon is implied thereby. The known production of lactic acid suggests that the depositon of this acid or its hydrogen ions on the muscle fiber is the cause of the raised surface tension. As to the cause of tonus in muscle, Bayliss advances the view that it may be due to a prolonged remaining of the acid. The work of Sherrington has shown the presence in voluntary muscle of phenomena similar to those in smooth muscle, and the author's work has shown that heat production is very small.

The second aspect of the excitation process here noted is the accompanying increased permeability of the cell membrane with marked fall



in electric resistance. These electric phenomena in nerve and muscle are related to such phenomena in the heart and secreting glands. Starling has demonstrated that Hill's law, mentioned above, holds for the heart muscle, and that all the phenomena of the output of the heart in relation to arterial pressure, venous outflow, and so on, are to be explained by the various degrees of filling of the ventricle at the moment of systole. Since the electrocardiogram is a complex case of electric change in muscle fiber, the author doubts whether conclusions drawn from changes in the form of the curve have any great significance in interpreting various forms of the ventricular complex. As to the electric phenomena of secretion, it may be considered that there is a current flowing through the cell from lymph space to duct, which continues as long as osmotically active matter and a permeable state of the membrane of one end of the cell remain.

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**The Theory of Irritation, Doctrine of Development, and the Problem of Constitution.**

*L. Borchardt, Deutsch. med. Wchnschr., Leipsic, 48: 1197, Sept. 8, 1922.*

The question of erratic modes of reaction to stimuli as the foundation of pathologic constitutional types is at the center of clinical research into constitution, since we have learned to regard the nature of such types in general characteristics of the organism, i.e. in functional rather than in morphologic characteristics. The erratic mode of reaction manifests itself in various ways. Thus, in the skin and mucous membranes it shows itself in a tendency to inflammation, exudation, etc. Increased demands upon the nervous system, the blood-forming organs, etc., are at the bottom of vagotony, neuro-arthritis, etc. We are concerned with a reacting power to stimuli, which in this group of cases is increased (while it is diminished in asthenic tissues). The author designates these forms as "irritable constitution" or "status irritabilis." Another group is concerned with processes of development and retrogression, evolution, involution: subevolutionism (infantilism), perevolutionism (premature development), and senilism.

There may be a combination of these pure types. The author points out the relations between stimulus and reaction, which have been established by Virchow. Irritability is the criterion of the living cell. The activity provoked by the stimulus, which is usually of a triple nature, is concerned with the establishment, the formation, or the preservation of a part (function, nutrition, formation); hence physiologic and pathologic processes are divided into functional, nutritive or trophic, and formative or plastic. The author emphasizes the importance of Roux's theory of the 4 developmental periods in the problem of constitution: (1) that of the disposition of organs, (2) that during which hyperemia and also functional stimuli act to promote growth, (3) that of functional development, and (4) that of senile retrogressive changes. The body condition, or constitution, is derived from inherited dispositions and functional stimuli. Anomalies of the constitution result through deviating dispositions or an inherited erratic mode of reacting to normal physiologic, or to abnormal, stimuli. The mode of reaction may be

erratic from the start, or may become so through injurious influences. The reactions evoked by stimuli will vary according to the developmental period. Disturbances of function, i.e. of the special activities of the tissues, underlie asthenia and status irritabilis. The former is characterized by a diminished activity of the specific cell functions, while in the latter the special functional activity of the several tissues is increased. These variations from the reactive power change their character during life. Therefore, if it is permissible to conclude that increased or diminished function of the living substance underlies the constitutional disturbances of reactive power, asthenia and status irritabilis, it may be assumed from the outset that the disturbances which lead to subevolution (infantilism), perevolutionism and senilism, affect another life activity of the cell—either nutrition or formation. Data are available on the question of infantilism. Peritz has shown that the dystrophic form in particular can be traced to a lack of lipoids. Hence it can be explained as a disturbance of nutrition.

Alongside of the functional, or nutritive disturbances, there occur deviations in the body form. They cause the asthenic habit, the arthritic habit, etc. It is not clear at the present time to what extent they are constitutional disturbances. Constitutional disturbances depending only upon variations in bodily dimensions are characterized by derangement of form.

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### **Secondary Electromotor Properties of the Human Skin.**

*Erich David, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:101, June 19, 1922.*

There is a discrepancy between the values of the polarization counterforces, as theoretically determined by calculation and by experiment. Invariably only a small percentage of the applied tension is found, whereas theoretically the applied tension should be all but attained (Gildemeister). To clear up this contradiction, direct measurements were undertaken of the polarization tensions produced by the human skin. This value will be the more correct the shorter the interval between charge and discharge. To shorten this interval as much as possible, the author employed (1) the tuning-fork method, the subject being connected by a tuning-fork, first with the electric current, and then with the galvanometer; (2) a rotating reverser, and (3) Helmholtz's pendulum, for determining the polarization value immediately (about 1/10,000 second) after one short current impulse. The skin of the lower arm and the palm was connected by means of nonpolarizable electrodes and Ringer's solution (at room temperature) first with a current source of 2-14 volts, and then after a short interval (dispersion time) with the galvanometer for an equal period only (conduction time), the galvanometer having been adjusted by the intercalation of a variable current so that no deflection was brought about (method of compensation). After a dispersion time of 0-1/120,000 second, 90% of the applied tension was recovered with 2 volts, and 80% with 10 volts, if the current had passed through the body only for a few seconds. This tension must be interpreted as polarization tension, since no appreciable amounts were found either in the electrodes nor in a system

composed of electrodes and fluid containers. If the dispersion time increases, smaller values are observed, the loss amounting to 20-30% after 1/2000 second. The polarization tension of the body, which is most probably to be attributed to the skin, at first increases with continuing closure of the current, in low tensions for some minutes, and then remains constant, at higher tensions for less than one second, after which it declines. These experimental results agree with the changes of resistance calculated by Gildemeister.

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**The Theory of Secondary Electromotor Properties of the Human Skin. Postscript to the Study by E. David.**

*Martin Gildemeister, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:112, June 19, 1922.*

In this paper, the author presents the theoretic evaluation of the experiments carried out by his pupil David, whose investigations are of great physiologic importance. Up to the present, it had proved impossible to demonstrate directly the high polarization values postulated by Cremer's nucleoconductor theory of the nerves. In conjunction with his collaborators, the author has shown that the skin of frogs, mammals and man readily lends itself to such investigation because of its pronounced polarizability. David has now established the postulated polarization values by means of actual measurements. These new experiments also agree with certain other conclusions. Thus, the consumption of time which had been inferred for the genesis of polarization from the initial peak on the closing of a constant current has now been made accessible to experimental observation. The tensions which have been found are certainly not action currents, to judge by their magnitudes. Nor is ordinary electrostatic capacity responsible, as this is contradicted by the experiments with a corresponding model and by the quantitative relations. The times of discharge and the law of discharge for the condenser form a basis for the calculation of the capacity of the hypothetical condenser, and the latter, in its turn, for the calculation of the thickness of the dielectric. The values thus found are below 1 micron. It is therefore not admissible to regard the entire tissue layer, measuring some centimeters in thickness, as the dielectric. Thinner strata and cell-membranes would be less open to objection. The magnitudes of the values calculated for the latter are also improbable; but serviceable results are obtained by applying Krüger's theory of metallic polarization to the body cells furnished with only partially permeable membranes. In this way, the skin of mammals may be regarded as a polarizable formation, in which the double layers play an important part not only statically (concerning membrane potentials and colloid charges), but also dynamically, and, so far as the latter is concerned, not only for tangential effects (electrokinesis), but also for transverse effects, namely in regard to conducted currents, so far as they take up at first a considerable part of the current. The alteration of concentration is not felt appreciably until they are charged. But afterward, on the other hand, the new charge of the double layers disappears very quickly after the cessation of external influence. The polarization tension

demonstrated by previous authorities, which is of longer duration but of slight intensity, is dependent on the alteration of the membranes caused by the invasion of electrolytes.

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**Thermo-Electric Studies of Temperature Variations in Animal Tissues. I. General Considerations, Description of Apparatus and Technic.**

*George W. Crile, Helen R. Hosmer and Amy F. Rowland, Am. J. Physiol., 62: 341, Oct. 1, 1922.*

The authors have previously shown that the intracellular changes in excitation and exhaustion which in certain organs and tissues—notably the brain—are revealed by the microscope, are also manifested by alterations in electric conductivity. Since variations in functional activity indicate variations in oxidation, and variations in oxidation are manifested by variations in heat production, and since heat is a constant product of functional activity, the measurement of this temperature change may be of value. For if heat is a constant product of functional activity, then, if one can measure the progressive changes in the temperature of the various tissues and organs during the various phases of excitation and exhaustion under conditions identical with those formerly studied (by these authors) such findings may be checked up and linked with the clinical evidence.

In the authors' experiments rabbits were used. The thermo-electric apparatus consisted of Leeds and Northrup galvanometers of types R and H, with especially constructed copper-constantan thermocouples made of 5 mil wire twisted together and soldered. The recording junction was exposed, the leads being separated from each other and protected by concentric glass tubes, the ends of which were joined by dental cement. The junction was kept as small as possible and the protecting glass tubes were of the smallest possible caliber. These tubes were bent so as to facilitate their introduction into the particular tissue. The use of any metal in the construction of the thermocouples was avoided. The "cold" or constant junction of the thermocouple was immersed in a tube of oil suspended in a constant temperature bath, maintained at 39° C., thus bringing the whole range of temperature in the tissues studied upon the scale of the galvanometers. As the extreme range of temperatures involved in living rabbit tissues does not exceed 7° C., it is possible to measure variations by the direct deflections of a galvanometer of suitable sensitivity. In the authors' studies on 77 rabbits the effects of various agents and procedures were observed, the temperature variations in the brain being measured in every instance, in the liver in most of the animals and in the muscle and thyroid, each in 2 instances. By the use of the specially constructed thermocouples it was possible to measure temperature variations in living tissues to within 0.01° C. By means of the apparatus described the changes in the brain and other tissues of the rabbits in stimulation and exhaustion from various causes was observed and the findings correlated with the histologic changes and the alterations in electric conductivity established by the authors' previous researches.

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**Thermo-Electric Studies of Temperature Variations in Animal Tissues. II. Effects of Anesthesia; Electric Stimulation; Abdominal Trauma; Exposure of Viscera; Excision of Organs; Acid; Alkali; Strychnin; Diphtheria Toxin.**

*George W. Crile and Amy F. Rowland, Am. J. Physiol., 62:349, Oct. 1, 1922.*

Following the methods described in the preceding paper of this series, the animals were subjected to stimulation and exhaustion from various agents and the temperature variations produced by each were observed and recorded. Inhalation anesthesia produced a continuously progressive decrease in the temperature of the brain and the liver. Electric stimulation (the terminal wires being applied directly to the sciatic nerve) caused a change in the temperature of both the brain and the liver in opposite directions. Exposure of the viscera resulted in a precipitate decrease in the temperature of the brain. The introduction of water (hot) into the stomach increased the temperature of the brain and liver. Hepatectomy was followed by a continually progressive fall in the temperature of the brain, which was unchecked by any therapeutic measure. Adrenalectomy produced a rapid decrease in the temperature of the brain.

In one experiment the intravenous injection of hydrochloric acid was immediately followed by an abrupt rise in the temperature of the brain, amounting to  $0.7^{\circ}$  C. with an equally abrupt fall to  $0.56^{\circ}$  C. below the point at which the acid was injected. From this point there was a rapid and precipitous decline until death, which occurred 5 minutes after the injection. In another experiment 8 c.c. saturated solution of sodium bicarbonate were injected intravenously. During the injection the temperature of the brain rose  $0.5^{\circ}$  C.; a fall followed to a point  $0.5^{\circ}$  below that at which the injection was started. During the following 10 minutes there was a further gradual decrease of  $0.33^{\circ}$ . Regarding the effect of strychnin, in no instance was the temperature of the liver affected by the injection of strychnin. Following the administration of diphtheria antitoxin no significant change in the temperature of the liver was observed, but there were variations in the temperature of the brain.

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**Thermo-Electric Studies of Temperature Variations in Animal Tissues. III. Adrenalin.**

*George W. Crile and Amy F. Rowland, Am. J. Physiol., 62:370, Oct. 1, 1922.*

In this paper of the series the authors observed the effect on rabbits of the administration of 0.4 c.c. per kg. of 1:1000 Parke, Davis & Co.'s adrenalin. It was noted that the temperature of the brain and of the thyroid was increased by adrenalin, but the temperature of the liver and of voluntary muscle was not affected by the injection of this drug. In the absence of the liver the injection of adrenalin produced either (a) no change or (b) a diminution in the temperature of the brain. In the absence of the thyroid the reaction of the brain to adrenalin was diminished, while in iodized animals it appeared more promptly and was.



greater than in normal animals. In animals under ether anesthesia the reaction of the brain to adrenalin was greater than in normal animals; in animals under nitrous oxid anesthesia it was delayed and diminished.

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**Induction Currents as Stimuli. II. The Influence of Self-Induction on Stimulation by Break Currents.**

*Martin Gildemeister, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195: 142, June 19, 1922.*

In a preceding communication (1910), the author investigated the circumstances on which the effects of an induced break current depend, more especially in apparatus without iron core. The amount of electricity corresponding to the threshold stimulus was determined together with its dependence on the other variables, i.e. (given the primary current and the object) on the secondary resistance and the size of the induction coil. The amount of electricity corresponding to the threshold stimulus was described as "electricity requirement"; as to the size, only the secondary coil counts. The author came to the conclusion that the electricity requirement is inversely proportional to the resistance in the secondary circuit. This is expressed by the formula:  $Q = \alpha + b/W$ , where  $Q$  represents the electricity requirement,  $W$  the resistance of the secondary circuit, and  $\alpha$  and  $b$  constants;  $b$  expresses the steepness of the corresponding straight line, and its value apparently increases in proportion to that of the self-induction of the secondary coil. We should then have  $b = \beta p$ , and the equation would read:  $Q = \alpha + \beta p/W$ . So far, this formula had not received experimental corroboration, and the new experiments were undertaken for that purpose. Muscles of frogs were stimulated by descending currents, the electrode consisting of the combination: mercury-calomel-Ringer's solution-pointed gelatin plug. The threshold determinations confirmed the supposition that the self-induction  $p$  of the secondary coil is contained in the constant  $b$ , and that therefore the second equation is correct. On the basis of this result, it may be stated, with respect to the gaging of induction coils, that any quantities of electricity produced by apparatus without an iron core, which satisfy that equation, are equivalent in regard to physiologic stimulation, i.e. that they would cause threshold stimulation in any given object. The physiologic principles of this law cannot be determined until the time elements of the induction currents have been investigated, the observations so far recorded being contradictory and of no avail.

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**Saturation Tension and Its Significance with Special Reference to Electrolytes.**

*F. Kraus and S. G. Zondek, Klin. Wchnschr., Berlin, 1: 1773, Sept. 2, 1922.*

The transportation of solid and liquid substances in muscle is to be attributed to 2 processes: surface potential and oxidative chemism. The latter represents, in growth and transformation of energy, a metastable balance in the colloidal ternary system, viz. a critical mixture of liquid

(electrolyte). The restoration of the colloidal plasma structure of the contractile substance means, depending on its nature, either recovery or preparation for function. The leading back of the system from lability to a metastable condition of balance is brought about by an expenditure of work in which the electrolytes are essential factors. Analogous processes are seen in secretion. Reversal of the process leads to taking up of fluid and turgor. The necessary energy is obtained by oxidation of the available organic acids. The surface potentials are subordinated to a vegetative system the parts of which are the membrane, the salt electrolyte, the hormones, exogenous and endogenous stimulating substances, ferments and the controlling vegetative nerve.

The potential is given from the proportion of membrane to salt electrolyte. Here extraordinarily complicated relations prevail, in which the varying charging with two antagonistic ion combinations, the potassium group, on the one hand, and the calcium group, on the other, plays a chief part, and on which the H and OH ions are dependent. An excess of calcium causes dissociation of H ions. So there develops, on the one hand, colloid electrolyte acidosis and, on the other, alkalosis. The K and Ca distribution in the membrane is an action of the vegetative nerves, in which the sympathetic with its relations to potassium leads chiefly to alkalosis of the membrane. These local changes in concentration of the cells are of special importance. Water also may act as an electrolyte and cause the setting free of H and OH ions. Potassium and calcium also cause a change in the direction of diffusion of water as an electrolyte as well as a change in permeability to anions and cations. The vegetative nerve has, in addition to the function of electrolyte distribution, a relation to chemism, for example, of creatin and cholin metabolism. Calcium, adrenalin and atropin supplement the action of the sympathetic. The influence of the vegetative nervous system on respiration, heat regulation, blood pressure, heart activity, blood distribution, secretion and transportation of water and solids is caused by regulation of salt electrolyte interchange.

In the centers of the vegetative nervous system there is a distribution according to 2 maximal scales. In the total vegetative nervous system the nature of the water displacement according to its dependence on the surface potential and the condition of the membranes are of special importance. Electrolyte combinations and irregular osmosis are to be considered in this, in the form of electrocapillary phenomena and electro-endosmosis. The vagus and sympathetic attract certain electrolytes. The surface tension is of considerable importance. Thus comes about the internal pressure of the cells and its variations, which correspond to turgor. The authors have studied these questions experimentally on living and isolated specimens and, by chemical examination for acidosis and alkalosis as well as production of bio-electric currents, they have shown the changes. Action currents and deformation currents are shown in curves. This shows the analogy between the action of potassium and the action of the vagus, on the one hand, and between the action of calcium and that of the sympathetic, on the other. After the addition of adrenalin, a picture develops similar to that of calcium, and muscarin, on the other hand, works like potassium.

The authors think that the results of these experiments may be utilized in the study of heart valve lesions. Their electrocardiograms also indicate relations of the sympathetic to the quick, and of the vagus

to the slow, fibers of the motor apparatus of the heart. Further studies show pictures of deformation currents and the influence on them of potassium and calcium, as well as electrolyte deviation, electrolyte inversion and electrolyte accommodation. Electrolyte turgor seems to be of importance in the pathology of diseases which are related to the vegetative nervous system, and in certain diseases of metabolism (protein and sugar metabolism, purin metabolism, gout), as well as in affections of the endocrine system. Antagonistic electrolytes may have an influence in the development of edema. Exhaustion, muscle tonus, is dependent on electrolytes. Electrolytes play a part in the pathology of the heart, especially in exhaustion of the heart and certain cases of individual types of reaction, particularly such as occurred during the war, also in heart hypertrophy and decompensation. Vagolability is frequent in heart patients, as the authors' clinical experiments have shown. Potassium and calcium experiments on the frog's heart give interesting analogies to conditions in organic heart diseases, particularly with reference to compensation.

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**Studies in Absorption from Serous Cavities. IV. On the Passage of Blood-Cells and Granules of Different Sizes through the Walls of the Lymphatics in the Diaphragm.**

*R. S. Cunningham, Am. J. Physiol., 62:248, Oct. 1, 1922.*

For the experiments here reported young adult cats of uniform size and weight were used; 30 c.c. of a mixture of erythrocytes (obtained from a chicken and carefully washed), large unfiltered carmin granules, and very fine lampblack granules, made up in isotonic sodium chlorid solution, were injected into the peritoneal cavity of each animal. The animals were killed at intervals varying from 1 to 30 minutes, and the diaphragm and anterior mediastinal glands were examined histologically. It was found that after 3 minutes' exposure all 3 types of material had reached the anterior mediastinal glands, and at this time the granules were not phagocytized, but practically all were free in the sinuses. In the experiments in which the exposure was 5-10 minutes there was a very small amount of phagocytosis to be seen in the sinuses of the mediastinal glands. This phagocytosis had evidently taken place in situ, because in the same experiments there were no cells with granular inclusions to be found in the lymphatic lacunas or vessels of the diaphragm itself. In these localities all the granules were free in small clumps and masses. With increasing intervals of time more and more granules were found within both free and fixed cells in the lymph-glands, until at 30 minutes the majority of the carmin and ink granules had been phagocytized; but the greater part of the red blood-cells still remained free in the sinuses of the lymph glands. In the lacunas of the diaphragm only a few phagocytic cells were discovered at this time. Careful examination of the peritoneal side of the diaphragm showed the lacunas in large measure filled with cells, ink and carmin, and both the mesothelial surface-cells and the endothelial cells of the lymphatics were found to contain numerous particles of ink and carmin. These experiments do not prove, the author says, that the vital red passed through openings between the cells, but might equally well indicate some

change in the permeability of the cytoplasm brought about as a result of the dilatation. These experiments are of special interest in regard to the findings reported here because, if the passage of the vital red particles takes place through physical openings temporarily produced between the cells, one then has an approximate measurement of the size of these openings. And if any of the absorption into the diaphragmatic lymphatics takes place in a similar manner, then the ability of the lymphatic endothelium to separate and form intercellular spaces is many hundred times greater than that of the blood vascular endothelium. Such a hypothesis does not seem likely, the author believes, and in consequence at present it seems more justifiable to accept the idea of absorption taking place through the cellular cytoplasm.

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**Studies in Absorption from Serous Cavities. V. The Absorption of Particulate Matter from the Peritoneal Cavity of the Fetus.**

*R. S. Cunningham, Am. J. Physiol., 62:253, Oct. 1, 1922.*

The fetuses used in this series of experiments were between 50 and 120 mm. in length. Cats were found to give the most satisfactory results and were used exclusively. The pregnant cat was anesthetized and through an abdominal incision the pregnant uterus was delivered. The fetus was rotated until the abdominal region was held between thumb and finger when the needle of a hypodermic was plunged through both the uterine and abdominal walls with a single stroke. About 1 c.c. of a suspension of lampblack or India ink was injected into the peritoneal cavity and the needle removed. The uterus was returned to the abdominal cavity of the mother and the incision closed. In some cases all the fetuses were left until the end of the experiment, in others they were removed at intervals. The method of removal was to incise the uterus and deliver the fetus, the abdominal cavity of the fetus was then immediately incised in order to prevent the few spasmodic attempts at respiration from having any effect on the abdominal contents. The head was severed from the body as quickly as possible, the fetus eviscerated, the diaphragm rinsed gently with warm Locke solution, the chest opened, and the entire thorax plunged into the fixative. Dissections were made after fixation had been allowed to progress for several hours. Smears were occasionally made from the peritoneal contents and fixed in methyl alcohol for study of cell types and amount of phagocytosis. The tissues were generally fixed in formalin, Bouin's or bichlorid acetic. Suitable control experiments were carried out on kittens a few days old. The author found that the absorption of particulate matter from the peritoneal cavity via the diaphragmatic lymphatics becomes active at a period at which the fetus begins to make respiratory movements. With increase in age, and consequent increase in the activity of the movements of the fetus, the amount and rapidity of absorption increases; and after birth there is a still further and even more decided increase despite the fact that many of the fetuses examined by the author were probably within a very few days of parturition. The conclusion seems warranted that in the fetus the pseudorespiratory movements are a most important if not the principal factor in starting and maintaining the absorption of

particulate material via the diaphragmatic lymphatics. The evidence obtained also indicates that the principal part of the granular material passes through the cytoplasm of the serosal lining cells and not between them, and that very little if any is absorbed by the agency of the leukocytes. Finally, the even distribution of ink granules over the surfaces of the serosal cells and the location of most of the intracellular granules in the region of the cytoplasm adjacent to the nucleus, suggest that the particles adhere to the surface quite generally and diffusely, and that the movement of the diaphragm against the liver and other viscera generally tends to force the granules by pressure into the cytoplasm of the cells.

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**A Convenient Automatic Apparatus for Experiments with Surviving Organs.**

*P. J. Hanglik and Floyd De Eds, J. Lab. & Clin. Med., 7:751, Sept., 1922.*

The apparatus consists of an electrically heated brass chamber with inflow and outflow for the physiologic solution, and contains a small brass tube for admission of oxygen or air, a thermometer, and an adapted heart lever for recording movements of the excised organ on a kymograph. The chamber is clamped on an iron support and to this is screwed a pine board for attachment of a 3 contact switch and a resistance lamp, which maintains the temperature at a constant level of 38° C. In addition there is a glass leveling bulb for the physiologic (Tyrode, Locke or Ringer) solution, which is conducted to the inflow of the chamber by rubber tubing. The arrangements for heating, removal and replacement of the solution are practically automatic, requiring a minimum of time and effort for manipulation.

The apparatus is simple, compact, easily transferable, permanent and inexpensive. Its important advantages for mammalian tissues are that warming of the organ or tissue is rapidly accomplished, which facilitates the initiation and maintenance of functional activity and recovery from previous effects, overheating is practically impossible, and the organ is not exposed to the atmosphere during washing, or removal of solutions. The apparatus can also be used for amphibian tissues.

**CIRCULATORY SYSTEM**

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**The Physiology of the Mammalian Auricle. IV. The Nature of Muscular Contraction in Auricular Fibrillation and Flutter.**

*Carl J. Wiggers, Am. J. Physiol., 62:310, Oct. 1, 1922.*

In this article the author presents numerous myograms of auricular fibrillation. Concerning them he says that by careful relation of the optic myogram, curves recorded from points 16-20 mm. apart on the auricle to ventricular ejection and filling on the one hand, and to the intrinsic electric deflection recorded from the same points, it is possible to separate the waves due to active contraction phenomena from those passively caused or influenced by ventricular activity. In pure or slightly impure flutter, each excitation wave is followed after a fairly

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constant latent period (0.04-0.05 second) by a coördinated muscular contraction differing from normal in its slower gradient, smaller amplitude, shorter duration, and a certain variability in amplitude. In pure flutter, groups of waves of different size obtain from time to time, but successive beats are fairly regular; in simpler forms of impure flutter the contractions vary in amplitude from beat to beat. In high degrees of fibrillation the auricle no longer responds to separate excitation waves. Under such circumstances it may be surmised that the fractions excited at one time are so small in number that the auricle practically becomes a conducting rather than a contracting structure.

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**The Active Response of Capillaries of Frogs, Tadpoles, Fish, Bats and Men to Various Forms of Excitation. I. Excitation by Electricity.**

*Tsang G. Ni, Am. J. Physiol., 62:282, Oct. 1, 1922.*

The purpose of these experiments was to ascertain whether capillaries actively respond to localized stimulation, so the unipolar method of electric stimulation was employed to study the effect of direct, localized excitation on the blood capillaries of frogs, tadpoles, fish, bats and men. Their active response was detected by observation with the microscope. Induced as well as direct currents were employed. Single make and break shocks did not cause visible effects; a summing series was required to elicit a response. Capillaries of the web of frogs and of the caudal fin of fish responded to a tetanizing current, and to a series of induction shocks. They also responded to the direct current, when a series of excitations was employed. Capillaries of the bat's wing were seen to respond only once to a tetanizing current, but they reacted to separate induction shocks and to the direct current. Capillaries of the human skin did not react to a tetanizing current, but responded to separate induction shocks. They reacted also to the direct current when a series of excitations was used. The fact that the reaction to stimulation was strictly localized would seem to justify the conclusion, the author believes, that the result was an active response of the wall of the capillary.

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**Vasodilator Mechanisms. I. The Effect of Nicotin on the Depressor Reflex.**

*S. W. Ranson, Am. J. Physiol., 62:383, Oct. 1, 1922.*

In Ranson's experiments cats under ether were prepared for carotid blood pressure tracings. Both vagi were cut low in the neck, their central ends secured by ligatures and carefully protected against drying or contamination. The ulnar and median nerves were exposed, included in a single ligature, and cut distally. In most experiments the vasomotor reflexes from stimulation of the vagus were first tested, then nicotin was administered intravenously and the reflexes tested during the period of paralysis and again after recovery from the effects of the toxin. In others nicotin paralysis was induced first and the vagal vasomotor reflexes registered during the paralysis and in various stages of recovery. The author's graphic results show that the drop in blood pressure from

weak stimulation of the vagus, which he interprets as evidence of active vasodilatation, is readily eliminated by nicotin. Furthermore, every trace of a depressor reflex from even strong stimulation of the vagus can be eliminated without giving an excessively large dose. This demonstrates that if the vasodilator fibers of the dorsal roots participate as efferent fibers in this depressor reflex the impulses which they carry pass through a synapse of sympathetic character.

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**Vasodilator Mechanisms. II. The Vasodilator Fibers of the Dorsal Roots.**

*S. W. Ranson and W. D. Wightman, Am. J. Physiol., 62: 392, Oct. 1, 1922.*

The present series of investigations was begun to determine whether any vasodilator impulses do actually pass from the spinal cord to the blood-vessels of the limbs and, if so, along what fibers they leave the cord. Dogs of varying size and age were anesthetized with ether and morphin. Tracheotomy was performed, both vagi cut, laminectomy was done, the dura opened, cord ligated at level of sixth lumbar segment, and the right sixth and seventh lumbar and first sacral dorsal roots ligated separately and cut close to the cord. In other dogs after the cord had been ligated a thread was passed under each of these 3 dorsal roots and the corresponding ventral roots were severed. In these cases the dorsal roots were ligated and cut after the plethysmograph had been applied. By means of a plethysmograph "stocking" pulsations and volume changes in the animal's leg were recorded. The authors' results (recorded graphically) confirm the conclusions of other workers that the dorsal root contains vasodilator fibers. After the lower lumbar and first sacral dorsal roots had been divided close to the spinal cord, a moderately strong faradic stimulus applied to one of them just distal to the cut caused a dilatation of the blood-vessels of the hind limb. The best results were obtained from the seventh lumbar and first sacral dorsal roots and by mechanical rather than electrical stimulation.

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**Vasodilator Mechanisms. III. The Vasodilator Action of Nicotin.**

*S. W. Ranson and W. D. Wightman, Am. J. Physiol., 62: 405, Oct. 1, 1922.*

In the authors' experiments anesthetized dogs were used. The abdomen was opened through the linea alba, the left abdominal sympathetic trunk extirpated and the right internal iliac artery prepared for the injections according to the technic described. After the abdominal incision had been closed arrangements were made for taking a blood pressure tracing from the carotid artery and a plethysmograph tracing from the left leg. On account of the hemorrhage and thrombosis that follows piercing the arterial wall with the hypodermic needle, it was necessary to develop a special technic for these injections. After opening the abdomen in the median line the right external iliac artery was doubly ligated and cut between the ligatures. The right internal iliac was followed into the pelvis, doubly ligated, and cut as far from its

origin as possible. The middle sacral artery and the lowest lumbar vessels of the right side were ligated. An opening was made in the right flank and the free end of the internal iliac artery drawn through it. The lower margin of the incision in the flank was stitched to the psoas muscle. The median abdominal incision was then closed. When everything was in readiness for recording the carotid blood pressure and volume in the left leg, a clamp was placed on the right internal iliac artery some distance above the ligature and a large hypodermic needle, the point of which had been converted into a bulbous extremity, was tied into the artery. The part of the artery distal to the clamp was then washed out with 4% sodium citrate solution. A syringe containing the solution to be injected was then attached and the pressure in the syringe and distal part of the artery raised above that of the general blood pressure. The clamp was then removed and the fluid forced slowly into the artery. Immediately after the injection the clamp was re-applied to prevent any blood getting into the cannula.

The authors found that when nicotin is injected into the arterial blood stream going to the leg it causes marked vasodilatation and swelling of the leg. Since this occurs when all nerve fibers running to the limb from the spinal cord and sympathetic trunk have been severed, it must be peripheral in origin. That the action is specific is shown by the fact that after repeated doses of nicotin have paralyzed this dilator mechanism nitroglycerin, acetylcholin and adrenalin still produce their characteristic vascular changes.

## DIGESTIVE SYSTEM

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### **The Reticulo-Endothelial System and Its Relations to Bile-Pigment Formation.**

*L. Aschoff, Münch. med. Wchnschr., 69: 1352, Sept. 15, 1922.*

The author believes that bile-pigments are formed not in the liver cells but in the reticulo-endothelial cells and in the histocytic elements. These, or the ferments produced by them and given off into the blood, are held responsible for the catabolism of hemoglobin and bilirubin, not the liver cells, which in all probability are only the places of secretion of the bile-pigments. The expression "reticulo-endothelial metabolism apparatus" should only indicate this partial system of organ and cell complexes taking part in metabolic processes and emphasize the system as such. The author warns against overexaggerating the importance of this system, and agrees fully with Minkowski when he demands that the reticulo-epithelial apparatus be limited to the field where it belongs. The same demand should be made for the liver cells, whose involvement in the production of bile-pigments, in spite of all the talk of its advocates, has never been proved.

## METABOLISM

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### **The Excretion of Carbon Dioxid by Relaxed and Contracted Sea-Anemones.**

*G. H. Parker, J. Gen. Physiol., 5: 45, Sept. 20, 1922.*

By means of an Osterhout respiratory apparatus the author measured the metabolism of the sea anemone *Metridium marginatum* Edw.

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in 4 states, relaxed, relaxing, contracted, and contracting. The basis of measurement was the number of hundred-thousandths of a milligram of carbon dioxide excreted per second by a gram of living sea anemone. It was observed that the process of relaxing and the states of relaxation and of contraction are accompanied by no unusual metabolism, but in the operation of contracting the metabolism becomes about half again as intense as that characteristic of the other states. The maintenance of the contracted state in *Metridium* for days at a time without an increase of metabolism indicates, the author says, that its musculature is of the type known as tonus muscle.

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**Enterotropic Uric Acid. II.**

*Theodor Brugsch and Julius Rother, Klin. Wchnschr., Berlin, 1: 1729, Aug. 26, 1922.*

The authors demonstrated 50 mg. uric acid in 1000 gm. fistula bile, and 200 mg. in 1000 gm. gall-bladder bile; the actual value must lie higher. As gall-bladder bile, fistula bile and duodenal bile cannot be compared with one another on account of their different concentrations, the authors have introduced the fiction of reducing enterotropic uric acid. By demonstrating the pigment content by the colorimetric method of Hijmans van den Bergh, they found that 1000 c.c. of duodenal bile with a pigment content of 0.1 gm. is to be regarded as normal, and they reduced the uric acid values of the different kinds of bile to correspond to this. Uric acid is obtained from bile by a modified precipitation with silver, which often fails in concentrated gall-bladder bile. The reduced enterotropic uric-acid value lies between 0.1 and 0.2 gm. in the fasting condition, and in exogenous administration of nuclein it may be considerably higher. For the fasting value, the relation of urotropic to enterotropic uric acid is 2: 1. In peroral administration of purin bodies, only one-third is excreted as urotropic uric acid, the rest as urea. The deficit may be explained by the theory of enterotropic uric acid, which is broken up in the intestine, not absorbed by the intestinal wall, and excreted as urea. In gout, less of the uric acid of the nucleins consumed is excreted urotropically than in normal conditions and the urea curve of the deficit runs a slow course, evidently because the liver excretes the enterotropic uric acid more slowly.

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**The Effect of Mineral Water on Carbohydrate Metabolism by Yeast.**

*Paul Mayer, Biochem. Ztschr., Berlin, 131: 1, July 29, 1922.*

Mineral waters do not have a uniform effect on carbohydrate metabolism, owing to various factors. Glucose in Carlsbad water undergoes a decomposition on irradiation but not without irradiation. Under the influence of Carlsbad water there is an enrichment of the organism in mineral constituents, particularly phosphates. Sugar metabolism in the animal body runs parallel with that in the yeast cell. On the administration of alkaline constituents—mineral water—a change can occur

in normal sugar cleavage in the animal body, causing a splitting into acetic acid, ethyl alcohol, carbonic acid and glycerin. This decomposition of sugar, designated as the third form of fermentation, occurs to a marked degree after the use of Carlsbad water and its salt. Greatly decreased amounts of alcohol and greatly increased amounts of glycerin are produced. The action of the sodium bicarbonate in the Carlsbad salt is increased by the sodium sulphate that is also present. Sodium chlorid also promotes the action, similarly to Glauber's salt, though to a somewhat weaker degree. The aforesaid simple salts, sodium sulphate and sodium chlorid, alone have no effect on the form of sugar catabolism. If Carlsbad salt is taken the rise in glycerin is 500% as compared with saccharose alone dissolved in tap water.

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**Remarks on E. Knaff-Lenz's Article on Blood Saccharase and Antigenic Properties of Yeast Saccharase, with a Contribution on the Appearance of Saccharase in the Blood Plasma after Parenteral Administration of Cane Sugar.**

*Emil Abderhalden, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:283, Aug. 24, 1922.*

Different authors have reported negative results with reference to the possibility of the blood plasma splitting cane sugar when this is administered parenterally, but Knaff-Lenz denies these conclusions. There were some positive cases, but in most experimental animals the results were negative. The author believes that after the parenteral administration of cane sugar, saccharase may appear in the blood plasma, but he succeeded only in exceptional cases in inducing this condition. The surprisingly quick appearance of saccharolytic characteristics in the blood plasma indicates that the saccharase is not newly formed but that it is carried to the blood from elsewhere. The negative results can probably be explained by the fact that in these organisms no saccharase was available. Probably certain conditions have to be fulfilled in order that pancreatic and intestinal saccharase in an effective form may pass from the intestine into the circulation.

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**Fermented Beverages and New Ideas Concerning Nutrition.**

*L. Randoïn and P. Portier, Bull. Soc. scient. d'hyg. aliment., Paris, 10:345, June, 1922.*

Nearly all the caloric value of fermented drinks is derived from the ethyl alcohol. In ordinary, moderately strong red wine, the alcohol supplies 94% of the total heat of combustion. Such a wine contains 80 gm. alcohol per liter, yielding 566 of the total 606.1 calories. The value of 600 calories per liter is only little below that of 1 liter of fresh grape juice. The small loss resulting from fermentation is offset by the superior keeping qualities. Alcohol is almost entirely burned in the tissues. If a daily dose of 1-1.2 gm. per kilo of body weight is not exceeded, provided it be taken in dilution, preferably at meals, alcohol does not produce intoxication, but a slight and useful stimulation. The abuse of fermented drinks increases the effect of alcohol on the nerve



centers, and harmful consequences follow. The potential energy of alcohol is transformed into kinetic energy within the body as completely as with ordinary foods. Alcohol cannot furnish a food reserve. However, it favors its production and permits other foods to supply the reserve. Wine probably owes part of its effect to catalytic substances. Fermenting liquors contain vitamins B and C, as do probably fully fermented beverages. Guinea-pigs rendered almost moribund by feeding superheated vegetables and bran, have been cured with red or white wine. A pigeon similarly rendered polyneuritic has been cured with red wine. The results so far are not conclusive.

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**The Metabolism of Inorganic Salts. I. The Organic Ion Balance of the Blood in Parathyroid Tetany.**

*Erwin G. Gross and Frank P. Underhill, J. Biol. Chem., 54: 105, Sept., 1922.*

An attempt was made to follow the inorganic constituents through the various stages of parathyroid tetany to determine whether there was a disturbance in the balance of the elements. Dogs were used as experimental animals and normal values in the blood were determined after a 48 hour fasting period. The removal of the entire thyroid-parathyroid structures was carried out under aseptic conditions and the animals fasted throughout the period of the experiment. Blood was obtained from the external jugular vein by aspiration, and the chlorids, total phosphorus, calcium, potassium, sodium and magnesium content was determined. The tabulated results show that the blood salts in dogs under normal fasting conditions are practically constant. Parathyroidectomy chiefly disturbs the ratio between calcium and potassium. Changes in the ratios are more important than the absolute changes in any one of the elements. When the ratio of the monovalent:divalent ions reaches 40 and above, the animals always show convulsive tetany, while a ratio (K):(Ca) of 10 or above is accompanied by convulsive tetany. The authors suggest the hypothesis that both low calcium and high potassium are factors in the production of the increased irritability.

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**The Mineral Content of the Normal White Rat during Growth.**

*G. Davis Buckner and A. M. Peter, J. Biol. Chem., 54: 5, Sept., 1922.*

The object of these experiments was to determine the mineral content of the carcasses of normal white rats at different ages. The data were desired for comparison with similar data to be procured under a change of the minerals ingested. Three rats were bred and only those litters from which 3 males and 3 females could be selected for analysis were used in the experiment. When the rats reached the desired age they were chloroformed and thoroughly washed with distilled water and dried. The esophagus, stomach, intestines, and rectum were dissected out and discarded. The remaining portions of the 3 rats of each

sex were weighed together and ashed. A composite sample of the ash was analyzed for calcium, magnesium, phosphorus and potassium. The tabulated results show that rats coming from a common parent stock, all similarly fed and having existed under identical conditions, have an individual variation in growth and mineral content in both males and females, which is not overcome when results are compiled from the average of 3 of each sex.

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**Dietary Factors Influencing Calcium Assimilation. III. The Comparative Efficiency of Timothy Hay, Alfalfa Hay and Timothy Hay plus Calcium Phosphate (Steamed Bone Meal) in Maintaining Calcium and Phosphorus Equilibrium in Milking Cows.**

*E. B. Hart, H. Steenbock, C. A. Hoppert and R. M. Bethke, J. Biol. Chem., 54:75, Sept., 1922.*

The authors experimented with 3 animals, all fresh milkers: a pure-bred Holstein, a pure-bred Guernsey, and a grade Holstein. The animals were confined to metabolism stalls for a total period of 13 weeks with quantitative collection of the excreta. None was with calf although all were bred during the experimental period. A definite daily aliquot of feces, urine and milk was composited for a period of 7 days, and analyses for phosphorus and calcium were made upon these composite samples. The daily feed for each animal in Period 1 (4 weeks) was timothy hay grown on an acid soil (10 lb.), corn silage (20-25 lb.), and a grain mixture of 60 parts yellow corn, 15 parts oil meal, and 25 parts wheat bran (about 1 lb. for each 3 lb. milk produced). In Period 2 (4 weeks) the timothy hay was displaced by 10 lb. alfalfa hay; the corn silage remained the same; the grain mixture was changed to 70 parts yellow corn, 25 parts wheat bran, and 5 parts oil meal, the daily allowance remaining unchanged. In Period 3 (5 weeks) the first ration was again fed, but with addition of steamed bone meal in amounts to make the calcium content of the ration practically equal to that of the alfalfa ration or feed mixture used in Period 2. All the animals received distilled water and common salt throughout the periods. The tabulated results show that cows producing from 30-45 lb. milk daily were in negative calcium and phosphorus balance on rations composed of grains and their by-products, corn silage and timothy hay. Alfalfa hay reduced the losses but did not bring about calcium and phosphorus equilibrium; negative balances continued, contrary to the authors' earlier observations when positive calcium balances were obtained with alfalfa hay. The latter was cured under caps, while the alfalfa used in the later experiment was cured in the windrow with exposure to air and light for 4 days. These differences in effect may be attributed to a difference during the curing process in the degree of destruction of the vitamin that assists in calcium assimilation. Supplementing the timothy hay with bone meal did not establish positive calcium and phosphorus balance or even equilibrium, although the losses were reduced as compared with the unsupplemented timothy hay. Blood calcium was comparatively high (20-25 mg. per 100 c.c. blood serum) during the timothy hay period when the calcium losses were greatest. In the alfalfa period it dropped to approximately 10 mg. per 100 c.c., but rose again to 16

mg. during the timothy hay plus bone meal period. With 2 other groups of cows not in metabolism stalls, one group receiving timothy hay or low calcium feedings, and the other alfalfa hay or liberal calcium feedings, no such difference in the blood calcium was observed. Inorganic phosphorus in the blood was low during the timothy hay period, but considerably higher in the alfalfa and timothy hay plus bone meal periods.

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**China as a Field for the Study of the Nutrition of Human Teeth.**

*J. F. McClendon, J. A. M. A., 79:1133, Sept. 30, 1922.*

Animal experimentation has shown that the chief factor in the well-being of the bones and teeth is diet. The Chinese diet is vegetarian, supplying in sufficient quantity everything needed in nutrition. The Chinese have little dental caries. The teeth require all those food elements needed by the body as a whole and in addition the elements giving them their hardness, chiefly calcium, fluorin and the phosphate ion. The metabolism of bones and teeth is similar. Thyroxin, exercise, burning with ultraviolet light and perhaps exposure to cold and some other agencies, increase the metabolism and phosphorus intake at a given growth weight and in this way tend to prevent rickets. Cod-liver oil in some way increases the phosphorus retention. In contradistinction to phosphate starvation, calcium starvation produces osteoporosis or light weight bones without gross rachitic lesions at the epiphysis.

With the diet of human beings it is difficult to say whether calcium or phosphate is most often deficient. Modern milling of cereals has been developed during centuries with the white man, but has been partially introduced into China only during the last 10 years. The excessive use of milled cereals is perhaps responsible for the greatest shortage of calcium phosphate in our diet. It is rather notable that China furnishes 2 fruits which contain the most perishable vitamin C in large amount and which will withstand high temperatures and drying; these are the orange and the peach, and there is strong evidence that they originated in China. Animal experiments tend to show that the effect of diet on bones and teeth can be worked out with comparative ease, and there is no reason why the same cannot be applied to human bones and teeth.

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**Food in Mental Work. Remarks on the Article of Kestner and Knipping.**

*Karl Bornstein, Klin. Wchnschr., Berlin, 1:1794, Sept. 2, 1922.*

The author argues against the statement of Kestner and Knipping (SURVEY, September, 1a—189) that mental workers should eat much meat and calls attention to the mental output in certain occupations. He recommends vegetable or milk proteins as being cheaper, and opposes the too great importance attached to meat at the present time. Vegetable food tends to make the reaction of the blood more alkaline.

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**The Importance of Meat in Nutrition.**

*Otto Kestner, Klin. Wchnschr., Berlin, 1:1795, Sept. 2, 1922.*

The author replies to Bornstein that the man who does muscular work needs more calories than the man with a sedentary occupation, 2800-4000 calories as against 1900-2400, but that both need at least 70 gm. protein. While with a calory intake of 4000, the protein can be given chiefly in vegetable form, it cannot be given thus to the sedentary worker with his lower caloric requirements, as with the necessary amount of protein the caloric value would be considerably increased. The increase of mental workers in the total population, the decrease of muscular work through the agency of machines and skilled workmen, and the great degree of satisfaction of hunger by meat, which leaves the stomach slowly, make milk products and meat necessary for a constantly increasing part of the population.

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**The Specific Dynamic Action of Various Food Factors.**

*Graham Lusk, Medicine, 1:311, Aug., 1922.*

Increased metabolism, according to Lusk, is due to the interrelation between the foodstuffs brought by the blood stream and the metabolizing cells themselves. His investigations of this problem are summarized as follows: When 50 gm. glucose is given to a dog it is rapidly absorbed and glucose molecules are furnished to the body cells in increased number. All sugars diffuse into the body cells very rapidly. Increased movement of unoxidized glucose molecules in diabetes does not influence heat production. The deposition of glycogen does not increase heat production. If 50, 75 or 100 gm. glucose be given to a dog, it is possible to increase heat production by 20% above the basal metabolism during the hours of glucose absorption, but increasing the quantity of glucose ingested does not increase the level of metabolism, which may, therefore, be described as the optimum level of glucose metabolism. Another dog, whose metabolism had been raised 30% above the basal level after 50 gm. glucose, suffered an increase of 35% after 70 gm. glucose, and one of 37% after 50 gm. fructose. It is suggested that, whereas part of the 50 gm. glucose could have been laid down as glycogen and removed from the circulation, all the fructose must first break up into methylglyoxal radicles, thereby increasing the mass of these readily oxidizable metabolites.

If carbohydrates be administered in excess, they may be converted into fat, but this process transpires with only a slight energy loss and does not appreciably increase the total cellular heat production which has already reached its maximum. Lactic acid being directly derivable from glucose may satisfy the cellular affinities for the latter so that administration of both these substances does not affect the total metabolism to any considerable extent. When acetic acid or alcohol is given with glucose, the metabolism is raised by the sum of the increases which each substance given alone would induce. Possibly acetic acid and alcohol are not glucose metabolites. The ingestion of large quantities of glucose does not reduce the CO<sub>2</sub> combining power of the blood;

acid metabolites, therefore, are not causative of the increased heat production.

During the conversion of carbohydrates into fat, there is a largely increased elimination of  $\text{CO}_2$  without the concomitant increase in metabolism. Therefore, an increase in  $\text{CO}_2$  production cannot be a stimulus to increased heat production. The transmutation of fructose into glucose, presumably through methylglyoxal, does not increase metabolism in the dog made diabetic with phlorizin. The mere presence of unoxidized intermediate fragments of fructose has, therefore, no influence on metabolism. Though there is a reduction of the  $\text{CO}_2$  combining power of the blood plasma after the ingestion of  $\text{HCl}$ , it has a very slight effect upon metabolism as compared to that induced by glucose. When a dog is made to run at the rate of 3 miles per hour, the additional energy production for the unit of work is slightly more without food than when 70 gm. glucose are given. From these facts, Lusk concludes that in the presence of a sufficient quantity of oxidizable fragments of carbohydrate metabolism, the heat production is raised to a higher level. Definite affinities for carbohydrate consumption are satisfied which are not involved where the extra supply of glucose is being continually depleted under the influence of work or is reduced, as in fasting, when the blood stream is under the regulatory control of the liver. The production of increased heat after carbohydrate ingestion is termed by Lusk the metabolism of carbohydrate plethora.

The influence of fat ingestion upon the production of heat was next studied by the author and he summarizes the results as follows: The administration of fat to a dog gradually increases heat production to a maximum in the sixth hour, when the increase above the basal level may amount to 30%. It then gradually declines reaching the basal level in 12 hours after its administration. According to Bloor, the sixth hour is the time of the maximum fat content of the blood. The additional heat produced is at the expense of fat oxidation. When glucose and fat are given together, the former is first oxidized, the heat production rises and the respiratory quotient approaches unity; the level of increased heat production continues through subsequent hours on account of the absorption of fat, the respiratory quotient declining on account of the increased oxidation of the latter substance. When glucose is given 4 hours after the ingestion of fat so that the maximum effect of glucose ingestion falls at the time of the maximum metabolism induced by fat, there is a summation of effect, the heat production reaching a level above the basal metabolism by the sum of the 2 several increments which each substance would have produced. The respiratory quotient indicates the metabolism of fat and carbohydrate. The same is true when glucose and acetic acid are given together. Therefore, in the presence of an amplitude of fat and of glucose molecules, the affinities entering into the mechanism of the increased destruction of either appear to be separate and different. The reason why fat, which is synthetically produced from carbohydrate, is not oxidized as is fat when ingested with carbohydrate, may possibly be that fat production from carbohydrate may be limited to a restricted area of tissue, whereas the oxidation of fat or of carbohydrate is a property of all tissues. The basal metabolism is independent of the height of the respiratory quotient, and, therefore, the basic requirement may be supported by isodynamic equivalents of fat or carbohydrate. The severity of diabetic



acidosis is no indication of the height of the metabolism in diabetes. From these facts, the same conclusion is reached regarding fat as regarding carbohydrate, that in the presence of an abundance of fat particles there is a metabolism of fat plethora, due to the utilization of fat by special fat-receptive cellular affinities.

The influence of protein upon heat production is summarized as follows: The extra heat produced by the specific dynamic action of protein may be used in substitution for the extra heat induced by the effect of environmental cold (Rubner). The increase in heat production is proportional to the protein metabolism at the time. It occurs when endogenous protein metabolism increases as in phlorizin glycosuria. A dog given 1200 gm. meat showed a maximum increase in metabolism of 88%; the increase remained nearly at this height during the first 10 hours after meat ingestion. Another dog, after taking 1000 gm. meat, showed an increase in metabolism of 93%. These quantities of meat were approximately the maximum which the dogs would eat. Fifty per cent. of the increased protein metabolized appears in the form of heat of specific dynamic action. When meat is thus given in excess of the nutritive requirements of the cell, there may be a retention of a part of the energy of the protein metabolized, deposited either in the form of glycogen or of fat, depending upon the condition of the glycogen reservoirs of the body. In man, the ingestion of 660 gm. meat caused a maximal rise in basal metabolism of 46%. Of the energy content of the increased protein metabolized, 75% appears in the form of the heat of the specific dynamic action. If the energy necessary to accomplish a given amount of work be determined before and after meat ingestion, it is found that the energy requirement for work in the first instance is superimposed upon the metabolism as induced by the specific dynamic action of protein in the second instance. This strictly differentiates between the character of the specific dynamic action of protein and of glucose. In this respect, alanin behaves exactly like protein and not like glucose.

Glutamic acid with its 5 carbon atoms has no specific dynamic action when given to a dog. Deamination and urea formation may, therefore, occur without increasing heat production. Aspartic acid behaves like glutamic acid, and so does succinic acid. Neither leucin nor tyrosin affects metabolism. The administration of 20 gm. glycoll to a normal dog is followed by a very great increase in heat production. Twenty grams of glycoll given to a dog diabetic with phlorizin, produced the same amount of extra heat in 4 hours as where the material was given to the same animal when normal, in spite of the fact that the ingested glycoll is completely converted into glucose and urea without oxidation. Glycoll neutralized with soda bicarbonate has the same effect upon heat production as when given alone. Bicarbonate alone has no influence on metabolism. Glycollic acid and sodium glycollate have little influence upon heat production. When glucose is given with glycoll or when the 2 combined are given at the height of fat metabolism, the total specific dynamic action of the mixture equals the sum of those quantities of extra heat production which each substance acting separately would have induced. Glycoll calories cannot, therefore, be substituted for glucose calories. Alanin behaves exactly like glycoll. These facts lead to the conclusion that the specific dynamic action of protein consists in a specific chemical stimulus of the cellular protoplasm,

which is independent of the oxidation of the material through which the stimulus is applied. It is termed the metabolism of amino-acid stimulation.

From this piece of research, Lusk restates a theory of metabolism which is merely a modification of that enunciated by Rubner. He believes that one is justified in the conclusion that the influence of food ingestion upon the basal metabolism of the quiet, resting cell may be upon 3 independent mechanisms within the cell: (1) a mechanism which is receptive to a chemical stimulus derived from amino-acids, such as glycocoll and alanin; (2) a mechanism of carbohydrate plethora which allows the metabolism of carbohydrate up to the limits imposed by self-regulation; and (3) a mechanism capable of receiving power from that quota of fat which, when in excess, increases the heat production of the cell.

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**Study of Vitamin B with Methods of Demonstration.**

*Sogen Tsukiye, Biochem. Ztschr., Berlin, 131: 124, July 29, 1922.*

A deficiency or absence of some definite chemical substance is regarded by many as the cause of polyneuritis in fowls. Since extract of rice hulls cures the disease it is assumed that the hulls contain a substance the lack of which causes beriberi. This substance was named water-soluble B or vitamin B by McCollum and Kennedy. Different theories developed as to the nature of this substance. Thus the disease was attributed to deficiency of albumin and salts (Eijkmann), of a protein of the prolamins group (Rosenheim and others), of phosphoric acids and phosphates, possibly phytin (Fraser and others), of phosphorus and potassium salts (Kilbourn and others), of nucleoproteids, derivatives of nicotinic acid, such as trigonellin or betain, of cholin and lecithin (Schaumann) and finally to absence or deficiency of one or more amino-acids (Roehmann). Vitamin B is said to bear some relation to the purin or pyrimidin bases or amino-acids. It is isolated from extract of rice hulls by first precipitating with tungsten phosphate or tannic acid to separate it with other bases from reducing substances. The vitamin is then separated from the other bases with silver nitrate and baryta. In order to separate out the metals, sulphureted hydrogen must be avoided and baryta must not be present in excess, and if alkaline, the solution must be heated. Before the hydrolysis the rice hull extract contains purin bases and amino-acids (but not histidin nor tryptophan), cholin (but not betain), glucose, levulose and different organic substances. Vitamin B cannot be precipitated by lead acetate from acid solutions. It can be completely precipitated by tungsten phosphate from sulphuric or hydrochloric acid solutions. It can be precipitated from silver nitrate solutions, but is again soluble in an excess of ammonia. It can be precipitated by tannic and picric acids. A part is precipitated by mercury bichlorid (but not by gold and platinum chlorid) as picrolonic acid. The biuret, Schmidt, Millon, Widal, xanthin, murexid and diazo reactions are all negative, but the Folin-Denis-McCollum uric acid reaction is weakly positive, but seems not to be specific. In a neutral solution vitamin is not soluble in alcohol of over 80%, in an acid solution it is slightly soluble in alcohol and water. Vitamin B is antineuritic and at the same time furthers growth. If larger

amounts are used than are necessary for antineuritic action, or if a certain amount is given daily, growth can be observed. It is very absorbable, especially by animal charcoal and metallic sulphids; it is completely dialyzable.

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**The Changes in the Para-Ocular Glands Which Follow the Administration of Diets Low in Fat-Soluble A; with Notes of the Effect of the Same Diets on the Salivary Glands and the Mucosa of the Larynx and Trachea.**

*Shinnosuke Mori, Bull. Johns Hopkins Hosp., 33:57, Oct., 1922.*

Previous work of the author has shown that the primary changes occurring in the eyes of rats on diets deficient in fat-soluble A are xerosis conjunctivae, and xerosis corneae. Since the primary change in the tissues is due to desiccation, it seemed logical to study the cause in the organs whose secretion moistens the conjunctiva normally. The author now reports changes in the lacrimal, meibomian, and harderian glands, in the mucous cells in the conjunctivas of animals in various stages of experimentally produced xerophthalmia, in the salivary glands and in the mucosa of larynx and trachea.

Findings indicate that lacrimal glands of such animals produce little if any secretion; there was cystic dilatation of the ducts of the meibomian glands; the harderian gland was markedly changed; and the mucous cells of the conjunctiva were nearly all destroyed. Secretions from all glands of the eye were much diminished or entirely lacking. Some or all of the salivary glands were found to be secreting not at all or very little, and the changes were those of xerosis in the eye. Other secretory organs as the liver, pancreas, bowel, kidneys, and thyroid showed no changes. The mucous membrane of larynx and trachea showed xerotic changes. Cod-liver oil (2%) added to the diet of the rats causes a disappearance of the xerosis. The fat-soluble A probably acts directly or indirectly on certain secreting glands to insure their normal function.

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**Experimental Rickets in Rats. VII. The Prevention of Rickets by Sunlight, by the Rays of the Mercury Vapor Lamp and by the Carbon Arc Lamp.**

*Alfred F. Hess, Lester J. Unger and Alwin M. Pappenheimer, J. Exper. Med., 36:427, Oct. 1, 1922.*

For the past year a large series of experiments have been carried out with sunlight and rays of different kinds under a variety of conditions. The investigation has included a study of the effect of variation of intensity, of transmission, or of reflection of light, of duration of exposure, of temperature, of the diet of the experimental animals, and the pigmentation of the skin, as well as other factors. For all experiments young rats about 40-50 gm. in weight were used. They were kept in a darkened room at all times. After an interval of about 21 days they were radiographed for the appearance of rickets at the epiphyses of the knee joints, and were killed after a total period of 25-28 days. The final criterion as to the presence of rickets was the histologic rather than the radiographic picture.

With sunlight, daily exposures of 15 minutes sufficed to protect rats, fed a standard rickets-producing diet, which was adequate in its calcium but deficient in its phosphorus content. The effect of sunlight may be stated to have been equivalent to about doubling the quota of phosphorus. A factor to be considered in employing heliotherapy in infantile rickets, is that the same degree of protection could not be obtained in November and December in rats on this diet. The effective rays of the sun, in the intensities studied, did not penetrate window glass. They manifested some protective value after reflection from a smooth white surface.

The rays from the mercury vapor lamp are capable of affording marked protection against rickets when given in small amount. With an alternating current of 160 volts, exposures of 3 minutes or less at a distance of 3 feet were found quite sufficient to accomplish this result. These animals failed to develop rickets in spite of the fact that the blood inorganic phosphate was far below normal. Irradiation before the animals were placed on the experimental diet did not delay the onset of rachitic lesions or decrease their intensity.

There are at least 3 factors which determine the effect of light—the diet, the rate of growth, and the degree of pigmentation of the skin. If 2 groups of rats, 1 composed of white and the other of black rats, are given the minimal protective dose of light, it will be found that although diet and rate of growth are the same, the black rats will develop rickets, whereas the white will show no rachitic lesions. It is manifest that the protective rays were rendered comparatively inert by the integumentary pigment.

A large number of experiments have been carried out with the carbon arc lamp. By means of this agent rickets in infants can be readily cured, and the cure is accompanied by a surprisingly rapid increase in blood inorganic phosphate. In a large series of young rats it was found that daily exposures of 3 minutes at a distance of 3 feet regularly prevented the occurrence of rickets. Light is able to prevent the occurrence of rickets in rats fed a rickets-producing diet characterized by a low phosphorus and high calcium content, or a high phosphorus and low calcium content. Moderate variations in temperature do not alter the effective action of light rays.

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#### **Experimental Rickets in Rats. VIII. The Effect of Roentgen Rays.**

*Alfred F. Hess, Lester J. Unger and Joseph M. Steiner, J. Exper. Med., 36:447, Oct. 1, 1922.*

In view of the fact that the rays of the sun, of the mercury vapor lamp, and of the carbon arc lamp are able to protect rats from rickets, it seemed worth while to test the protective value of soft Roentgen rays. In addition to these preventive tests, a series of rats was subjected to massive doses of Roentgen rays, with the object of possibly damaging the cells to such an extent as to lead to the development of rickets. The animals were on a rickets-producing diet while they were subjected to the action of the soft Roentgen rays. All the animals developed rickets, in spite of the irradiation, a result quite

contrary to that obtained when the mercury vapor lamp or the carbon arc lamp was employed. A series of animals was next subjected to very large doses of Roentgen rays. For this purpose a universal Coolidge tube was used, 8 in. distance, with 3 mm. aluminum as a filter, a spark-gap of 6 inches, and 5 ma. current. The exposures were for periods of 3 and 6 minutes. The diet was just sufficient to prevent the occurrence of rickets, but contained little phosphate in excess, so that if the intensive irradiation tended to produce rickets, it should be rendered evident on this diet. In no instance, however, did rickets develop, despite the extensive blood and bone-marrow changes induced by the intensive irradiation.

## RESPIRATORY SYSTEM

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**Comparative Studies on Respiration. XXIII. The Effect of Adrenalin on the Production of Carbon Dioxid by Animals and by Plants.**

*Dorothy M. Hutchinson, Am. J. Physiol., 62:192, Oct. 1, 1922.*

The adrenalin used in these investigations consisted of the dry product obtained from Parke, Davis and Co. The dry powder was dissolved in hot water (95° C.) and rapidly cooled to room temperature to check the oxidation which proceeds rapidly at high temperatures. The production of carbon dioxid was measured by means of the apparatus described by Osterhout. The rate of respiration was taken as the reciprocal of the time required to change the indicator from pH 7.78 to 7.60 and is expressed by the author as per cent. of the normal (which is in all cases taken at 10%). The plant material consisted of radish seedlings with caulicles  $\frac{1}{2}$ - $\frac{3}{4}$  in. in length. The animal tissue experiments were made with the muscles of winter frogs, the entire hind-leg being used after carefully removing the skin. The author's graphic data show that adrenalin has similar effects on the respiration of frog's muscle and of radish seedlings. Stronger solutions (0.002-0.003%) caused a depression. This was followed by a return to normal, probably due to the oxidation of the adrenalin. Weaker solutions produced a rhythmic effect; the rate of production of carbon dioxid fell, rose, then fell and rose again.

## NEUROMUSCULAR SYSTEM

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**The Appendages of the Brain.**

*W. D. Halliburton, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:1134, Sept. 9, 1922.*

The author discusses the hypophysis, pineal gland and choroid plexuses. The internal secretion of the anterior lobe of the hypophysis governs growth of the skeletal tissues, that of the posterior lobe raises blood pressure. Cells covering the choroid plexuses in the cerebral ventricles secrete the cerebrospinal fluid. The pressure of the latter is not the effect of transmitted arterial pressure although it may be modified by changes in vascular pressure. The volume of the craniospinal contents varies. The pressure of the cerebrospinal fluid is

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increased by excess of  $\text{CO}_2$  or lack of oxygen in the blood, by the volatile anesthetics and by an extract of the choroid plexus or brain. The extract contains a hormone acting directly upon the choroid secretory cells. Diffusible substances introduced into the cerebrospinal fluid rapidly enter the blood. Diffusion is most rapid in the sub-cerebellar region, slowest in the lower spine. The cerebrospinal fluid is unlike lymph. The membrane lining the cerebrospinal spaces admits substances passing from the fluid to the blood but is not permeable in the opposite direction except for oxygen. It is thus protective. The protein and sugar of the cerebrospinal fluid provide for nervous repair and energy.

The pineal gland is interesting chiefly from the standpoint of comparative anatomy. Its function as a primitive eye has been lost in man. The pineal gland was originally paired laterally. Anterior and posterior pineal structures are due to displacement. In *Sphenodon*, *Petromyzon* and *Geotria*, the pineal gland is not merely vestigial. It is most complex in the lamprey and lizard, which are not closely related. Its ocular structure is wholly lost in crocodiles and snakes.

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#### **Membrane Alteration and Nerve Excitation.**

*U. Ebbecke, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195: 555, Aug. 14, 1922.*

Despite numerous differences, the skin and the nerves possess one common property: both are strongly polarizable, and therefore in both an electric current causes a change in the concentration of the polarizable end-surfaces, the plasma membrane of epithelial cells, and the division between the "covering" and the "core" of the nerve fibers or fibrils. It has been determined for the skin that irritations alter the plasma membrane, making it more permeable and, therefore, less polarizable. The present study seeks to determine whether similar changes in the polarizability could be determined in the nerve, in other words, whether there is any relation between polarizability and excitability. The investigation deals with alterations of membranes before and after excitation. If a constant current is passed through a nerve so that one of the electrodes is adjacent to a dead portion of nerve, the resistance of the nerve for both directions of current is almost equal, when the current is very weak. With a stronger current, it is greater with the anode as the "different" electrode (i.e. connected with the normal nerve), than with the cathode. The stronger or more prolonged the current, the greater does anodal resistance become. With constant tension the current eventually increases if the cathode is the "different" electrode, and decreases if the anode is the "different" electrode. With very weak constant currents, the electrotonus produced by the passage through a nerve is nearly the same on the anode as on the cathode side. The stronger and more prolonged the current, the more strongly does the anelectrotonus predominate. When a portion of nerve is faradized with a strong alternating current, that part corresponding to the anode of the opening stroke becomes negative to the part corresponding to the cathode of the opening stroke. This after-effect, designated as negativity residue,

may last many minutes with strong currents. The threshold of stimulation of the sensitive cutaneous nerves is so altered by stimulation of the skin that the threshold for induction strokes and cathodé closure is raised, that for the anode opening is lowered.

From these findings the following conclusions are drawn: When a current passes through a nerve, the nerve membrane at the cathode is rendered more permeable, while at the anode it is rendered less so. This alteration of the membrane results in an altered polarizability of the nerves. The preponderance of the anelectrotonus depends on the greater polarizability of the denser anodal portion of nerve and is obliterated by all influences which render the nerve membrane more permeable. A reversible permeability of the nerve membrane can be produced also by electric, thermic, chemical or mechanical influences of greater strength. The portion of affected nerve is in a state of local parabiologic continuous excitation. The 3 stages of nonexcitability, diminished excitability and hyperexcitability, correspond to the different degrees of permeability of the membrane. This is demonstrated by the transition of the catelectrotonic increase of excitability to the depressive cathode action and temporary cathodal nonexcitability. The state of permeability of the membrane is indicated by a lowering of the opening threshold. In this condition ionic stasis to the degree which determines the exciting action of the cathode closure is more difficult to attain, while the equalization of engorged ions necessary for the anode opening effect is more easily produced.

The increase of permeability by the encroaching current is supposed to be related to the Nernst accommodation. This conception of the processes in the nerves renders possible a uniform interpretation of various electrophysiologic facts.

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**The Dissolution of the Curve of the Action Current in Striated Muscle into a Series of Disappearing Oscillations, and a Separate Period Peculiar to the Action Current in Tetanus.**

*A. Judin, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:527, Aug. 14, 1922.*

Under suitable conditions, the string galvanometer dissolves the monophasic curve of the action current into a series of disappearing oscillations. The tests were made by indirect stimulation of the gastrocnemious muscle of the frog, the string galvanometer having been rendered aperiodic. When the instrument is sufficiently sensitive, the curve of the action current shows 4 apexes and 4 oscillations lasting 0.006-0.007 second each. The first oscillation shows the maximum amplitude and lasts somewhat longer. If a nerve-muscle preparation receives 2 successive maximal stimuli at intervals beginning with 0.0009 second, and increasing by 0.0009 second, the curve shows an alteration from that resulting after single stimuli only beginning with an interval of 0.0036 second. It follows that the reception of a stimulus by the muscle is succeeded by a period of nonexcitability. The duration of this period lies between 0.0027 and 0.0036 second. Probably the period of nonexcitability occupies as much time as is required for the first oscillation to reach its maximum. After the first maximal stimulation, a

chemical process of maximum intensity and definite direction takes place in the muscle. This maximum cannot be augmented. But if the process occurs in the opposite direction, the new stimulus causes a reversion in the direction of the process. However, the tendency of the muscle to maintain the character of its periodic process, with a period of 0.006-0.007 second, causes the second action current to be delayed. This delay ceases as soon as the interval between the 2 stimulations is the same as the individual period of the muscle. The magnification of the mechanical and the electric effect parallels the increase of the stimulus. Even with incomplete tetanus (stimulation interval 0.04 second opening strokes) these 4 oscillations, and a fifth (weak) oscillation, can be seen; at times there may even be 6 oscillations. In order to produce a complete tetanic contraction, the stimulation must occur before the termination of the electric process evoked in the muscle by previous stimulation. An increase in the frequency of stimulation finally results in a number of oscillations, fairly constant (160), with a further diminution of the interval of stimulation. This yields a value of 0.00625 second per oscillation, which figure agrees with the curve.

To carry out these tests, it is necessary to reduce the resistance of the nonpolarizable electrodes as much as possible (electrodes plus muscle about 12,000 ohms) and the strings must not have too much resistance (silvered quartz strings of about 500 ohms).

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#### **Triple Motor Innervation of Striated Muscles.**

*E. Frank, M. Nothmann and H. Hirsch-Kauffmann, Klin. Wchnschr., Berlin, 1:1820, Sept. 9, 1922.*

The authors have retested the work of Boekes and Dusser de Barenne for the occurrence of accessory sympathetic fibrils and end-organs along with motor nerve fibers, and also the researches of de Boer and his followers, who assign to the sympathetic nerves the control of muscle tonus. While in unstriped muscle the cells are controlled by two autonomic antagonists, the authors' investigations show that in skeletal muscles the parasympathetic maintains muscular tonus, while the sympathetic inhibits it, in the same manner as in the bronchial tree, gastro-intestinal tract, and vesical and uterine cavities. Muscle tonus, being a spasm that appears after a definite period of latency and lasts for some time, can be produced in striated muscle only under abnormal conditions. Only lightning-like twitchings and rapid relaxation can normally be evoked after single stimuli, and tetanus after successive stimuli. Muscle tonus in the form of waxy flexibility occurs in skeletal muscles in decerebrate rigidity and in the pallidal syndrome (paralysis agitans, Wilson's disease, encephalitis lethargica). The autonomic nerves which Langley includes under the name of parasympathetic, arise from the midbrain and hindbrain and the sacral segments of the spinal cord; they are functional antagonists of the sympathetic, and like the latter they have an interposed ganglion cell from which the postganglionic fibers are trophically dependent. To the parasympathetic the authors add the vasodilators leading to the extremities from the posterior spinal roots, without passing through a ganglion cell.

The receptive apparatus of the end-organ of the parasympathetic has an identical biochemic structure and reacts electively to the same hormone. The sympathetic and adrenalin, on the one hand, the parasympathetic and cholin (or its ester), on the other hand, act upon the receptive apparatus. Acetylcholin (acetic acid ester of cholin), as a parasympatheticomimetic agent, acts as an antagonist to adrenalin; it stimulates glandular secretion, increases muscle tonus in the bronchial tree, gastro-intestinal tract, pupillary sphincter, bladder and uterus; in the cardiac innervation, it furnishes the inhibitory complex of vagus irritation; it causes the musculature of the arterioles to relax. By stimulation of the nerve trunks carrying the vasodilators, peculiar effects can be produced upon striated muscles after degeneration of their motor nerves. For example, after extirpation of the hypoglossal nerve, stimulation of the lingual nerve or of the chorda tympani evokes an extremely sluggish movement of the tongue musculature. After destruction of the facial nerve, stimulation of the ansa of Vieussens produces a peculiar slow movement of the muscles of the lips. Sherrington severed the anterior and posterior lumbar and the first 2 sacral roots, centrad to the spinal ganglion; a month later, electric stimulation of the ischiatic nerve (whose motor portion must have degenerated long before) produced slow contraction of the foot and toes, which outlasted the stimulus for a brief period. The authors also studied the antagonistic effects of acetylcholin and scopolamin upon the musculature of the tongue and extremities in animals. Four days after resection of the right hypoglossal nerve, the injection of 0.5-2 mg. acetylcholin exerted a tonic action upon the paralyzed half of the tongue, resembling stimulation of the lingual nerve. After section of this nerve, one-tenth of the original dose (0.1-0.2 mg.) sufficed to produce this effect since the inhibition of the homologous nerve influence results in much more intensive action of the electively mimetic pharmaceutic agent. In cats and dogs, with the femoral and ischiatic nerve severed, stimulation of the hind leg with acetylcholin evoked tonic contractions of the muscles of the paralyzed extremity, i.e. of the muscle groups deprived of their motor nerves. This effect was produced even 3 weeks after the posterior lumbar and the first sacral roots had been cut centrad to the spinal ganglion, and the corresponding anterior roots had been cut subsequently. Where scopolamin (6-12 mg.) was injected for its paralyzing effect upon the parasympathetic, the results were a prolonged latent period, fatigue, retarded nerve excitation and suppression of the acetylcholin effect. Division of the lingual nerve required greater amounts of scopolamin (0.03-0.0001 mg. acetylcholin) to produce complete inhibition, owing to the increased affinity of acetylcholin for the receptive substance. Novocain released tonus. When the electric irritability was undisturbed, the acetylcholin action was absent. Injections of dimethylguanidin, predisposing to spasm, influenced the acetylcholin effect by appearance of general spasms and repeated lingual tonus.

According to researches by the authors, tonomotor fibers occur in the chorda tympani, the ansa of Vieussens and the posterior roots which, like the vasodilators, belong to the parasympathetic. They could be demonstrated microscopically, for example, in the tongue (fibers of chorda tympani) and in eye muscles. The authors designate as "autonomic" nerve-fibers those fibers, probably nonmedullary in their last segment, which show characteristic fine end-rings and end-loops in

the motor end-plate or the end-plate of the end-organ itself. Of these autonomic nerve-fibers the parasympathetic are those which enter into relation with the cholinophil receptive substance of the muscle or gland cell. Parasympathetic nerves do not require the interposition of a peripheral, nicotin-sensitive ganglion cell. The parasympathetic nerves transmit accelerating impulses, even cause tonic contraction, contracture and probably also plastic rigidity and fixation of position of the striated muscle. A portion of these fibers is derived from the terminal cord of the sympathetic nerve, being probably inhibiting antagonists of the parasympathetic nerve. This is indicated by the authors' adrenalin experiments. The acetylcholin effect is designated as a "pharmacodynamic degeneration reaction," which is found only in the mammalian muscle. In mammals the discharge of tonic innervation is much reduced by the contact of the muscle with its motor nerve.

These phenomena throw light upon the interplay of tonus and tetanus of agonist and antagonist in the natural play of muscles. They can serve to clear up clinical manifestations, especially the gait in tabes and the movements in Parkinson's disease.

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#### **The Distribution of the Sympathetic Fibers in Peripheral Nerves.**

*Masuo Shimbo, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:617, Aug. 14, 1922.*

In connection with the question of the vegetative innervation of striated musculature, the discussion of which was also taken up by Kuré, under whose direction the present research was conducted, histologically different nerves were examined for their content of non-medullated fibers. To this end, the pieces of nerve were fixed in formol, in Müller's or Erlicky's fluid, and embedded in celloidin. The sections were mordanted with ferric chlorid, stained according to Weigert, and differentiated with borax-potassium-ferrocyanid. Cross-sections of the nerves reveal 3 kinds of medullated nerve fibrils—large, medium and small. Each of them is supplied with thick and thin medullary sheaths. The sympathetic fiber with neurilemma nuclei is easily recognized as a lighter zone. Some nerves contain so many of them that as much as one-fourth of the cross-sections may appear light. The phrenic nerve contains fewer of them in its radical portion, while in its lower cervical portion there appear numerous sympathetic fibers often united in bundles at the periphery. As a rule, the sympathetic fibers are not localized in foci, but are distributed profusely over the cross-section. In the phrenic and intercostal nerves they are more abundant than the medullated fibers. Moderate amounts occur in the nerves supplying the muscles of the back, in the femoral, peroneal, radial and tibial nerves; small numbers are found in the ischiatic, ulnar and median nerves. A certain parallelism exists between the numbers of sympathetic fibers in the nerve branches supplying the various muscles, and the creatin content of the muscles studied by Hoshino. Discrepancies are found only in the respiratory muscles.

The facts here described are another support for the acceptance of a tonic vegetative innervation of striped muscle.



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**Retardation of Conduction and Reduction of Metabolism as the Cause of the Apparent "Habituation" of a Nerve Paralyzed by Heat.**

*Walter Thörner, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195: 602, Aug. 14, 1922.*

The conducting power of a portion of nerve may be annulled by local heating up to a certain temperature, and will return upon cooling. As far as can be judged from muscular twitchings, the reestablishment is complete. If the test is repeated with the same portion of nerve, a higher temperature than that of the original test is required to cause the conductivity to disappear. This resistance of the nerve to the effects of heat is the greater, the higher the degree and the longer the duration of the original heating, within certain limits. This phenomenon is designated as apparent habituation. The ischiatic nerve of *Rana temporaria* loses its conductivity at approximately 35° C. When heated to 40°, the repetition of the test shows that it disappears only at about 38-39°. When heated above 40°, permanent injury to the nerve begins. The alterations of conductivity between 34 and 40° are irreversible.

On the one hand, the nature of this heat paralysis is regarded as suffocation, while the habituation to higher temperatures is traced to retarded metabolism, depending upon an altered colloidal state. If this interpretation is correct, it follows that the nerve accustomed to heat paralysis must also be more resistant to lack of oxygen. This could be proved experimentally. Retardation of metabolism in the nerve is expressed by a diminution in its rate of conduction. The question arises whether, after a severe heat paralysis of the nerve, there occurs, together with the habituation, a retardation of conduction which would persist after recovery and would recede together with the habituation during a period of rest and at room temperature. It was actually found that after heat paralysis, those portions of nerve which were not affected by it showed a prolonged period of latency (the increase averaging 47% of the original latency period). The nerve conduction is retarded 11.8% of the original rate. In general, the figures for the degree of habituation and for the retardation of conduction run parallel. That we are not here dealing with the effect of any death process is evident from the fact that, in addition to a marked decline of the phenomena of habituation, an undoubted increase in the rapidity of conduction could be determined. Complete rest at room temperature for a few hours caused both phenomena to recede more than one-half of their value.

Thus the view that the phenomena of habituation depend upon a retardation of metabolism limiting the oxygen requirements, has received a new support. Apparently we are dealing with reversible alterations of the nature of the protoplasmic colloids.

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**The Influence of Temperature and Other Factors upon the Two-Summitted Contraction Curve of the Gastrocnemius Muscle of the Frog.**

*Paul M. Harmon, Am. J. Physiol., 62: 261, Oct. 1, 1922.*

The author undertook this work to investigate the conditions under which the two-summitted curve appears, and if it proved to be

a normal phenomenon, the method of its normal control by the body. In the experiments the gastrocnemius muscle of the leopard frog, *Rana pipiens*, was used. The animals were pithed, the skin cut around the ankle joint and pulled up over the muscle. The Achilles' tendon was cut from its insertion and the gastrocnemius freed from its connection with the bone. The skin was again pulled down over the muscle and the ankle tied securely to the frog board. The knee was held stationary by a needle which was thrust through the knee-joint and into the frog board. A small window was cut in the skin over the upper part of the gastrocnemius and a nonpolarizable zinc-zinc sulphate electrode placed against the muscle. The nonpolarizable electrode and the copper wire running from the tendon to the muscle lever were connected to the secondary coil. The current was obtained from a storage battery of 2 volts. The lever was weighted with 10 gm. placed just beneath the attachment of the muscle to the lever. When the muscle was at rest it supported no weight, but care was taken to keep the copper wire taut. The author found that the normal simple contraction curve of the attached gastrocnemius muscle of the pithed frog is double-summited when the frog's temperature is between 16° and 23° C. When the temperature of the frog is above about 23° C. the curve is single-summited; below about 16° C. the two summits are fused to form an elongated, flat-topped, cold curve. The second summit of the two-summited curve is muscular in origin when the temperature of the frog is below about 18° C. It may be increased in height by repeated stimulation of the muscle or nerve and decreased in height by an increase in muscle temperature. When the temperature of the frog is between about 18° and 23° C., the second summit may be increased in height by small doses of strychnin, by repeated stimulation of the muscle or nerve, and by a slight decrease in muscle temperature. It may be caused to disappear by division of the sciatic or ninth spinal nerve; division of the posterior root of the ninth nerve; mechanical stimulation of the sciatic nerve; chemical or electric stimulation of the foot of the homolateral side; electric stimulation of the central end of the eighth spinal nerve, and by an increase in muscle temperature. The second summit of the curve seems to be very closely associated with muscle tonus and is probably caused by a contractile substance in the muscle which is different from that which causes the first summit.

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**The Importance of Blood Supply in the Functional Capacity of the Muscles.**

*E. Atzler and R. Herbst, Biochem. Ztschr., Berlin, 131:20, July 29, 1922.*

The true work of the muscle takes place independently of oxygen, but the latter plays a great part in the resting periods, and it has been thought that it has the task of oxidizing the lactic acid formed during work. Experiments were made to determine the changes in the work curve after limitation or complete interruption of the blood supply. In congestion the exhaustion fall was steeper and the height of the constant phase of the work curve lower. When the blood supply was interrupted the exhaustion fall was more rapid than in congestion, and in a short time incapacity for contraction developed. In congestion the

steepness of the exhaustion fall and the height of the constant phase changed in a definite proportion to the congestion pressure. The higher the congestion pressure, that is, the less the minute volume of the blood current, the steeper the exhaustion fall and the lower the constant phase. If after the blood supply has been cut off and the contracting capacity of the muscle has been lost, the blood current is again released, there is a rapid return to working capacity, the height of contraction corresponding to the minute volume which is now flowing through the vessels. If the work is not begun until some time after the blood supply is cut off, the exhaustion fall is steeper and the incapacity for contraction is attained quicker, the greater the interval between the application of the constriction and the beginning of the work. With a pressure of 180 mm. Hg in a Recklinghausen cuff no work was possible after an interval of 25 minutes. The beginning of incapacity for work after a long interval is dependent on the degree of pressure, which is explained by the gradual loss of functional capacity of the compressed nerve. The same conditions were found on electric stimulation.

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**The Transformation of Energy within the Muscle. VI. Origin of the Heat of Contraction.**

*Otto Meyerhof, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:22, June 19, 1922.*

If work is done by a muscle under anaërobic conditions, carbohydrates (glycogen) disappear, and an equivalent quantity of lactic acid is formed. Essentially the same process takes place if muscular rigidity is induced by increased temperature or by chemical action, and further, if the muscle is deprived of oxygen at a low temperature without stimulation, in which case the process is much slower. The general equation of this anaërobic phase of metabolism is  $C_6H_{10}O_5 + H_2O = 2 C_3H_5O_3$ . The number of calories per gram of lactic acid is 400. The combustion of 1 gm. glycogen produces 4191 calories, 0.9 gm. (corresponding to 1 gm. glucose) yields 3772 calories, and the heat of combustion for 1 gm. lactic acid has been calculated as 3661 calories. The difference between these values is 111 calories, whereas 400 calories were found for the reaction. The present inquiry aims to clear up this discrepancy. Hence, the heat of combustion of lactic acid was determined anew, 3615 calories being found for 1 gm., and 14 calories for the heat of dilution. The difference between the heat of combustion of glycogen and that of lactic acid in electric fatigue (at 14° and 22°) averages 370 calories; if sectioned muscles in a phosphatic solution are used for the determination, it is almost exactly 200 calories. The lactic acid, it should be added, is distributed equally between solution and muscle substance and is present in the phosphatic solution in diffusible form. The 200 calories almost correspond with the 157 calories calculated for the heat of cleavage of glycogen, the 14 calories for the heat of dilution of lactic acid, and the 19 calories for the heat of reaction with phosphates, yielding a total of 190 calories. The diminished production of heat in sectioned muscles is caused exclusively by the transition of the lactic acid into the solution, as is proved by the determination of the caloric quotient of rest anaërobiosis (experi-

ments on unskinned and skinned frogs). The heat of reaction of lactic acid in the interior of the muscle is to be attributed altogether or mostly to the hydrogen ion. On the introduction of valeric acid into the muscle, heat is produced without simultaneous production of lactic acid, namely 0.3 calory per gram of muscle, i. e. about half as much as in tetanic fatigue; but on the introduction of acetic acid ester, only 0.1 calory is formed per gram of muscle, and it is possible that this heat must also be attributed to split acid. The heat of reaction of lactic acid within the muscle (190-200 calories) may be interpreted principally as dependent on the heat of dissociation of protein. For in the neutralization of 1 gm. lactic acid by phosphates or carbonates, 20 calories are produced, whereas this amount is considerably increased in the case of fluids containing protein, such as blood serum, egg albumin, casein solution. If the heat of reaction of buffered amino-acids is examined, their reaction with lactic or hydrochloric acid results in the production of heat which may be interpreted as inverse heat of dissociation of the amino-acid, namely 130 calories per gram of lactic acid. Essentially the same heat is produced in solutions of serum albumin, serum globulin or myosin, free from basic salts, namely 137 and 140 calories, respectively, per gram of lactic acid, which makes it possible to calculate the heat of dissociation of the proteins for the acid dissociation as 12,350 and 12,600 calories. The heat of dissociation in the muscle amounts to 60 calories more, probably because deionization of the protein takes place in a nonaqueous phase or on structural surfaces. No secondary reaction was observed which might account for the missing 60 calories. No anaërobic carbon dioxid is produced, nor does lactic acid disappear in any appreciable quantity after the contraction. It is hardly probable that an anaërobic process has sufficient energy for the reversible conversion of lactic acid and carbohydrates and to produce, in addition, a positive excess of heat. The temperature coefficient of the formation of lactic acid up to 10° is between 2 and 3 in sectioned muscles, and near 4 in intact ones. The former value corresponds to the temperature coefficient of the isometric increase of muscular tension (Hill and Hartrel), whereas that of relaxation is 3.6, corresponding to the present figure for intact muscles. Since it may be supposed that the neutralization of the lactic acid with myosin does not take place in sectioned muscles, the correspondence of the temperature coefficients would seem to indicate that the formation of lactic acid must be referred to an increasing and not to a decreasing tension of the muscles.

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**Physiologic and Colloidochemical Study of the Mechanism of the Contracture of Striated Muscle Caused by Toxins.**

*Otto Rieser and S. M. Neuschlosz, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:190, Aug. 11, 1922.*

Gelatin in 0.5% solution was brought into contact with different toxins in 6 different H-ion concentrations (pH 8.4, 7.8, 7.0, 6.1 and 4.9 produced with buffer solution by Michaelis' method) in order to study the influence of these substances on acid intumescence. The

viscosity of the gelatin solutions was determined with Ostwald's viscosimeter. With veratrin, as in the other experiments, the following dilutions were examined: 1:1000, 2000, 4000, 80000, 160000, 32000, 64000, and 128000. Veratrin in low concentrations and with not too acid a reaction, furthers intumescence, in higher concentrations it decreases intumescence, the more so the more acid the medium. This helps to explain the action of veratrin. Thus the great delay in the descending branch of the veratrin contraction is regarded as an expression of the increased intumescence as well as of the delayed acid excretion and the lengthening of the intumescent stage caused by it. In a similar way the authors explain other peculiarities of veratrin muscle contraction.

The action of strophanthin (Boehringer) is similar to that of veratrin, viz. increase of viscosity on low, decrease on high concentrations. But the effectiveness of strophanthin increases throughout with an increase in H-ion concentration. This curve has an ascending and a descending branch and at a certain concentration runs through a maximum. This characteristic of strophanthin, transferred to the heart muscle, explains why the action of strophanthin begins quicker and is stronger the more frequent the heart beat. The H-ion concentration in muscle increases with the frequency of the heart beats, which favors the action of the strophanthin. Digitalin has the same action as strophanthin. But the increased action with the increase in acidity is not nearly so great as with strophanthin. If the observed action of digitalin is transferred to heart muscle the results are as follows: Low concentrations with favorable pH promote intumescence of the sarco-plasm, by which the contractions are made more energetic and effective. With higher amounts of digitalin the toxin is present in the limiting membrane in a detumescent concentration, which decreases the flow of acid through the thickened membrane and brings about a position of permanent contraction. Quinin decreases the viscosity of the gelatin in any concentration and any degree of acidity. The increase of muscle tonus after quinin may be regarded as a result of thickening of the membrane. Caffein in small amounts decreases the viscosity of the gelatin solution; in large amounts it increases it. The capacity of the albumin bodies for intumescence is increased by pH. This factor is not involved in muscle contracture. The caffein affects the processes of metabolism that lead to acidity of the tissues, which in turn support the direct action of the caffein on the contractile substance. Nicotin did not show any uniform action on the capacity for intumescence of the gelatin, and no relations could be found to the muscle action of this substance. Novocain always caused a moderate increase in the viscosity of the gelatin solution. The degree of action increases with the concentration of the solution as well as with its alkalinity. Morphin, codein and acetylcholin have no effect on the capacity for intumescence of the gelatin nor of the contractile substance of muscle. Atropin, which in itself does not have any marked effect either on muscle or gelatin, inhibits the action of veratrin both in the direction of favoring and decreasing intumescence. This characteristic is due to the fact that atropin displaces veratrin from its adsorption combination with the albumin bodies and replaces it. Novocain acts in quite a different manner; it favors intumescence to the extent that it overcomes the detumescent action of veratrin.



## URINARY SYSTEM

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**Studies on the Nervous Control of the Kidney in Relation to Diuresis and Urinary Secretion. VI. The Effect of Unilateral Section of the Splanchnic Nerve on the Elimination of Certain Substances by the Kidney.**

*E. K. Marshall, Jr. and Marian M. Crane, Am. J. Physiol., 62: 330, Oct. 1, 1922.*

The authors have previously shown that increasing the blood flow to the kidney (by section of one splanchnic nerve) caused a marked increase in the elimination of water and chlorids, a definite but smaller increase in that of urea, and practically no change in the output of creatinin and phenolsulphonephthalein. In this paper they report an extension of the work to the study of the effect of increased blood flow on sulphate, phosphate, carbonate, ammonia and hydrogen-ion concentration in the urine. The experimental procedure was the same as that described by the authors for their previous experiments. The authors found that increased blood flow through the kidney increases markedly the elimination of water, chlorids and carbonates, to a less extent that of urea, phosphates and sulphates, while the elimination of creatinin, ammonia and phenolsulphonephthalein is unchanged under the same conditions. The authors claim that these results agree most satisfactorily with a theory of filtration through the glomeruli, and reabsorption and secretion by the tubules.

## ENDOCRINE GLANDS

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**Note on the Abdominal Chromaffin Body in Dogs.**

*George B. Wislocki and S. J. Crowe, Bull. Johns Hopkins Hosp., 33: 377, Oct., 1922.*

In previous experiments suprarenal insufficiency was produced by repeated surgical operation, in the present study by a combination of surgical removal and the implantation of radium. Ten dogs so treated died and the abdominal chromaffin body of these was studied. Previous work by many authors has shown that the chromaffin body contains the same active principle as the adrenal medullar, and Kahn has apparently shown that the abdominal chromaffin body is a functioning organ actually liberating its secretion into the blood stream. The technic was that of Wislocki for the demonstration of the chromaffin.

It was found that in dogs in which the adrenals had been destroyed, the abdominal chromaffin body at death exhibited abnormal or slightly increased activity, and it would seem that this body is capable, in adrenalectomized dogs, of supplying that portion of the function of the adrenal glands subserved by the medulla. There is conclusive proof that the cortex is necessary for life, and these experiments prove that the medulla is not necessary to life, but they by no means demonstrate the same for the entire chromaffin system. This must be shown by further work.

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**Note on a Modification of the Chromaffin Reaction, with Observations on the Occurrence of Abdominal Chromaffin Bodies in Mammals.**

*G. B. Wislocki, Bull. Johns Hopkins Hosp., 33:359, Oct., 1922.*

That the original technic of Stilling and Kohn is sufficient to demonstrate chromaffin bodies in man, dog, cat, and rabbit, is shown by the work of a number of authors, but it has not been successful in some animals. The author modified the technic, and presents the results on certain animals. He succeeded in showing the presence of macroscopic chromaffin bodies in the retroperitoneal tissue of the opossum, squirrel, guinea-pig, and monkey.

The new technic consists in excising tissue from a freshly killed animal, washing it free of blood, and fixing in 90 parts of 3.5% potassium bichromate with 1 part of 40% formaldehyd for less than 3 hours; in 10% formalin for 24 hours, then washing and dehydrating in 60 and 70% alcohol. The tissue is then bleached from 6 to 24 hours in 70% alcohol, with 20 parts hydrogen peroxid and 10 parts water. When fully bleached, tissue other than the chromaffin bodies is white, while the chromaffin bodies stand out as lemon-yellow to dark-brown patches.

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**Effect of Adrenalin and Extracts of Pancreas and Liver on Blood Dextrose.**

*Ellison L. Ross and Lloyd H. Davis, J. Pharmacol. & Exper. Ther., 20:121, Sept., 1922.*

Dogs were used in this work. The effect of 0.25 c.c. epinephrin (1:1000) per kilogram of animal, injected into the leg vein, brought on a hyperglycemia in every animal; in 15 minutes the amount of blood sugar was much greater than at the end of an hour. The average glycemia before injection was 0.840% dextrose; 15 minutes after injection it was 0.1364%, and 1 hour after it was 0.1098%. There was an increase of 62% in 15 minutes, and in 1 hour the increase was only 31% above normal. The fresh pancreatic extract brought on a decrease in the blood sugar in every case except 1, and in this 1 the increase was only 0.007%. The group of animals averaged before injection 0.0910, 15 minutes after, 0.706, and 1 hour after injection, 0.0962%. There was a decrease in the blood sugar of 23% at the end of 15 minutes, and an increase of 5% at the end of an hour. When the fresh pancreatic extract was injected, followed immediately by adrenalin, in each case, both for the periods of 15 minutes and 1 hour, there was an increase, except in 1 observation, that for the hour period for the last animal of the series. The average before the injection was 0.0954% while 15 minutes later it was 0.1330 and 1 hour after injection it was 0.1040. In 15 minutes after injection of these 2 substances the blood dextrose increased 39% and in 1 hour the increase was only 9%.

When the incubated mixture of pancreas and adrenalin was administered, the tendency was toward a reduction in the glycemia at the end of 15 minutes, but at the end of an hour the tendency was

upwards. The average glycemia before injection was 0.099%, 15 minutes later 0.091% and at the end of an hour 0.1028%. In order to determine whether or not this property of pancreatic extract was not the property of an extract of any parenchymatous organ, similar work was done with preparations of liver. The extract of liver alone brought on slight increases, 4% in 15 minutes and 13% in 1 hour. There was no characteristic fall in glycemia from the liver preparation such as occurred from the injection of pancreatic preparation. When both adrenalin and liver preparations were injected at the same time, there was present the characteristic increase of adrenalin, and, added to it, that of the liver preparation.

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**Vascular Reaction to Epinephrin in Perfusates of Various**  
**CH. II. The Portal-Venous System of the Liver.**

*C. D. Snyder and L. E. Martin, Am. J. Physiol., 62:185, Oct. 1, 1922.*

One of the organs of the body of chief interest in connection with the rôle of the hormone of the medulla of the adrenals is the liver. This paper deals with the results of perfusing the terrapin's liver with saline solutions of various  $C_H$ , with and without minimal amounts of the Takamine preparation. The immediate object of the present experiments was to determine the effect of these solutions upon the rate of outflow from the hepatic veins with the inflow cannula inserted into the portal vein, and with the hepatic arterial supply cut off. The terrapins were pithed as to brain and upper part of spinal cord. The ascending vena cava and the coronary vessels of the stomach were ligated. The gastric vessels were tied to prevent an uncontrolled seepage into the liver. By inserting a wide outflow cannula into the sinus at the gateway to the atria, with the 2 descending venae cavae tied at their junction with the sinus, with the ascending vena cava tied as high up as it could be reached without injuring the liver, with the gastric vessels tied off and the inflow cannula in the portal vein, the liver of the terrapin is almost completely isolated from the rest of the body.

The solutions were made up of glass redistilled water containing 0.6% NaCl, 0.03% KCl and 0.02% calcium chlorid, to which was added minimal constant amounts of monosodium and disodium phosphates in the proportions necessary to maintain the various concentrations of H-ion desired. Tests at the end of the experiments demonstrated that the  $C_H$  remained constant in the various perfusing bottles. These tests were made by the colorimetric method, using phenolsulphonephthalein against standard tubes. The head of pressure of the perfusing fluids was kept constant by the use of Mariotte's bottles. This was set to equal about 10 cm. of a water column. The solutions were put in 4 reservoirs the contents of 2 of which were adjusted to a H-ion of lower and that of the other 2 to a H-ion of higher concentration. To one of each of these 2 pairs adrenalin-Takamine was added to a concentration of about 1:10. One of the two adrenalin-free solutions, usually the one of lower pH, was used first to wash out the blood from the liver and to get the organ adjusted to the fixed conditions of the experiments. This was allowed to perfuse for several

minutes. The method of recording the hepatic outflow was for the drop method. From the drops recorded the outflow for the various solutions could be reduced to a minute-volume denomination for comparison. In order to get a fair record of the effect of a new solution it was necessary to allow the fluid to perfuse the liver 4-7 minutes before recording. The duration of the record itself was about 2 minutes. After the perfusions were in progress for 1½-2 hours the usual edema characteristic for a Ringer's solution made its appearance, when the experiment was discontinued. In all, 10 animals were experimented upon. In general these experiments have shown that changes in the H-ion concentrations of a perfusing fluid will determine whether a minimal dose of epinephrin shall be pressor or depressor, excitatory or inhibiting in its action.

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**The Liberation of Epinephrin during Muscular Exercise.**

*F. A. Hartman, R. H. Waite and H. A. McCordock, Am. J. Physiol., 62:225, Oct. 1, 1922.*

The authors have previously described experiments in which it was indicated that epinephrin was released during the development of fatigue from muscular exercise. In this paper they report a continuation of those experiments, employing a technic similar to that already described. The authors' studies on the animals (cats) embraced records of pupil dilatation; denervation of the adrenal; the denervated eye reaction as a test for epinephrin in muscular exercise; latent period for secretion increase; the magnitude of dilatation; after-secretion of epinephrin; the amount of epinephrin released; effect of adrenalin injections on muscular activity; effect of adrenalin on fatigue convulsions; epinephrin release during "warming up" and "second wind." The authors used 50 cats in the study of the relation of the adrenals to exercise. Injections of adrenalin into intact animals appear to be most beneficial in exercise if given intramuscularly. When injected subcutaneously it is absorbed too slowly, while injected intravenously it is quickly destroyed. Intramuscular injections are absorbed in large enough amounts over a prolonged period to simulate more nearly the increased output during exercise and therefore appear to be most beneficial. The authors' experiments show that the increased dilatation of a denervated pupil (superior cervical ganglion removed) during exercise is due to epinephrin. The latent period for the beginning of the increase in epinephrin during vigorous exercise must be less than 1½-3 minutes. The increase appears much later in mild exercise. The maximum output of epinephrin depends upon the intensity and duration of the exercise. After the exercise ceases the increased output of epinephrin persists usually for a few minutes, and after vigorous exercise of long duration sometimes for a few hours. The increase is gradually diminished until it disappears altogether. Adrenalin injections usually, although not invariably, improve the working power of the individual, the authors found. These improvements resemble the second wind which is observed in normal cats accompanying dilatation of the denervated pupil. The injection of adrenalin hastens the

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onset of fatigue convulsions, but in the authors' experience these convulsions developed most easily in cats which were very easily excitable, while clumsy lethargic animals were not subject to them.

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**Studies of the Thyroid Apparatus. VII. A Differential Effect of Thyroparathyroidectomy and Parathyroidectomy on the Incisor Teeth of the Albino Rat.**

*Frederick S. Hammett, Am. J. Physiol., 62:197, Oct. 1, 1922.*

In the author's experiments 80 rats were used. Of these Group 1 consisted of 20 rats, Group 2 of 26 rats and Group 3, the control group, of 34 rats. Group 1 consisted of thyroparathyroidectomized animals; Group 2 of parathyroidectomized animals; Group 3 of normal controls. The rats were operated on at 75 days and dissected at 150 days, at which time the number of rats with dental defects was noted to be: Group 1, 1 rat; Group 2, 20 rats; Group 3, none. The dental defects consisted of fragility and hollowing out of the teeth. The author's opinion is that the apparently specific dental defects following parathyroidectomy but not following thyroparathyroidectomy are peculiar expressions of a summation of stimulation of metabolism. They seem to indicate that the parathyroid function is in some way connected with calcium metabolism, but they do not indicate that this connection is direct, the author believes.

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**A Study of the Distribution of Iodin between Cells and Colloid in the Thyroid Gland. IV. The Distribution of Iodin in the Hyperplastic Thyroid Gland of the Dog after the Intravenous Injection of Iodin Compounds.**

*Harry Benjamin van Dyke, J. Biol. Chem., 54:11, Sept., 1922.*

The author having found that there was relatively little difference in the ratio of the percentage of iodine in cells to the percentage of iodine in whole gland in dog thyroid glands exhibiting great variations in histologic appearance and iodine content, undertook this study to determine what effect acute iodization of hyperplastic thyroid glands had on the ratio value. Dogs with thyroid glands usually definitely hyperplastic were used in all of the experiments. Under light ether narcosis the solutions of KI and thyroid colloid were injected into the femoral vein. Every effort was made to section the glands as rapidly as possible after their removal from the animal. In determining the ratio of the percentage of iodine in dried cells to that in dried whole gland a modification of the method first described by Tatum was employed. The quantitative determinations of iodine were made by Kendall's method.

Author's tabulated results confirm the findings of Marine and Feiss and Marine and Rogoff that the hyperplastic thyroid gland of the dog rapidly binds iodine intravenously introduced as a solution of KI. The ratio value of iodine in cells to iodine in whole gland was found to be very low after the intravenous injection of KI solution into dogs with hyperplastic glands, when those glands were removed 1.5-60 minutes after the injection. The ratio value more nearly approached the



normal if the interval elapsing between injection and removal of gland was made about 24 hours instead of 1 hour or less, as in most of the experiments. When iodine as colloid iodine solution of normal animals was administered intravenously practically none of the colloid iodine was taken up by hyperplastic glands during the periods of time used in these experiments; yet from an injection of a comparable amount of iodine in the form of KI the ready binding of iodine by similarly hyperplastic glands was proved. Colloid iodine of hyperplastic glands removed 1 hour after the intravenous injection of KI solution was taken up to some extent by hyperplastic glands, but these glands bound additional iodine as KI introduced after the colloid iodine injection. The author thinks the incompletely synthesized active principle is probably more diffusible and more readily split into simpler products than active principle fully synthesized.

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**The Apparent Occurrence of Proteinogenic Amins in the Thyroid Gland.**

*Ubaldo Sammartino, Biochem. Ztschr., Berlin, 131:219, Aug. 11, 1922.*

Experiments have not definitely determined whether the iodine-containing proteins of the thyroid gland and their iodine-containing tryptophan split product (thyreotoxin) is identical with the internal secretion of the thyroid gland. In the internal secretions, 4 known aromatic proteinogenic amines (phenylethylamine, p-oxyphenylethylamine,  $\beta$ -indolethylamine and  $\beta$ -imidazolethylamine) enter into consideration. These readily originate from the corresponding amino-acids through the action of putrefactive bacteria, and in order to avoid this, only fresh thyroid glands were used. From the extracts of these substances crystallized in alcohol, inositol was first obtained, and after separation of the alcohol, the extract was dissolved in water and treated in a bicarbonate alkaline solution with benzoyl chloride. The precipitate obtained did not crystallize; in ether it separated into 2 fractions, one soluble and the other insoluble. Both were boiled with concentrated hydrochloric acid on a sand bath with reflux cooling in order to drive off the benzoyl groups. This was then diluted with water, the split-off benzoic acid was separated with ether and the hydrochloric aqueous solution was evaporated. The residuum was dissolved in water and precipitated with dilute picric acid. A very minute amount of a crystalline substance (histamine) resulted; after careful neutralization with a solution of caustic soda, additional slight crystallization occurred in the mother liquor, the melting point of which corresponded with that of tyramine picrate; finally there was another fraction, the melting point of which was identical with that of phenylethylamine picrate. These minute traces of the 3 proteinogenic amines bore no relations to the large amounts of the original substance. It cannot be said, therefore, that the proteinogenic amines of the aromatic group are the effective portion of the albumin-free thyroid gland extract. Indolethylamine, which readily betrays its presence by the glyoxylic acid—sulphuric acid reaction in an absolutely albumin-free solution, is not contained in the very fresh gland. With a positive result of the reaction, it is well to investigate whether a base, tryptophan itself, or a derivative is present;

with a negative result, the presence of the entire group may be assumed. The belief, based on the identity of effect of the albumin-free extracts of the thyroid gland, and the effect of the proteinogenic amines, that the chemical combinations are identical, is untenable.

## 1b. BIOLOGIC AND ORGANIC CHEMISTRY

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### **Cataphoretic Charges of Collodion Particles and Anomalous Osmosis through Collodion Membranes Free from Protein.**

*Jacques Loeb, J. Gen. Physiol., 5:89, Sept. 20, 1922.*

The author has shown in previous communications that when a salt solution is separated from pure water by a collodion membrane, water diffuses through the membrane as if it were positively charged and as if it were attracted by the anion of the salt in solution and repelled by the cation with a force increasing with the valency. In this paper, measurements of the P. D. across the membrane are given, which show that when an electrical effect is added to the purely osmotic effect of the salt solution in the transport of water from the side of pure water to the solution, the latter possesses a considerable negative charge which increases with increasing valency of the anion of the salt and diminishes with increasing valency of the cation. Measurements of the P. D. between collodion particles and aqueous solutions were made by the method of cataphoresis, which prove that water in contact with collodion particles free from protein practically always assumes a positive charge (except in the presence of salts with trivalent and probably tetravalent cations of a sufficiently high concentration). The author also shows that the product of the P. D. across the membrane into the cataphoretic P. D. between collodion particles and aqueous solution accounts in general semiquantitatively for that part of the transport of water into the solution which is due to the electrical forces responsible for anomalous osmosis.

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### **The Influence of Electrolytes on the Cataphoretic Charge of Colloidal Particles and the Stability of Their Suspensions. I. Experiments with Collodion Particles.**

*Jacques Loeb, J. Gen. Physiol., 5:109, Sept. 20, 1922.*

In the author's experiments on the cataphoretic P. D. of collodion particles, the particles were prepared as follows: Merck's solution of nonflexible collodion in alcohol and ether was poured into water and stirred with a glass rod. A spongy mass of solid collodion accumulated around the rod. The solid collodion was washed a few times with water and dried with filter paper. A strong solution of this collodion was then made up in chemically pure acetone (about 10 gm. in 100 c.c.) and water was then added until a light cloudiness was formed. The acetone was then removed from the solution by distillation under reduced pressure, and the remaining milky fluid was centrifuged. The sediment, when stirred up with water, gave a concentrated suspension of collodion particles. The suspension was cen-

trifuged and the larger particles in the sediment were used. In the author's experiments two drops of the concentrated suspension of collodion particles were added to 50 c.c. of the various solutions used, and this dilute suspension served as material for the mobility measurements. The collodion particles moved toward the anode, thus indicating that they were negatively charged. Only in the presence of salts with trivalent cations, like  $\text{LaCl}_3$ , was the sign of charge reversed. In the author's experiments it was found that the P. D. between the collodion particles and water was a minimum when the water contained no salts, and was as near as possible to the point of neutrality. When acid, alkali, or a salt was added the P. D. rose rapidly with increasing concentration until a maximum was reached. This maximum depended on the nature of the electrolyte added. It was high when the anion was plurivalent and the cation univalent, and low when the cation was plurivalent and the anion monovalent. The influence of acid, alkali, and salts with monovalent ions, e.g.  $\text{HCl}$ ,  $\text{NaOH}$  and  $\text{NaCl}$ , was not very different. Upon the addition of increasing concentrations of electrolytes the P. D. rose, reaching a maximum, and then dropped again upon a further rise of concentration.

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**Cell Penetration by Acids. VI. The Chloro-Acetic Acids.**

*W. J. Crozier, J. Gen. Physiol., 5:65, Sept. 20, 1922.*

The author's several previous articles on this subject have provided measurements of the apparent rates of penetration of integumentary cells of the nudibranch *Chromodoris zebra* by different acids. In the present report further data are presented (in graphic form) in continuance of this inquiry. The chloro-acetic acids were used, in conjunction with redeterminations of penetration curves for acetic and for hydrochloric acids. The author believes that measurements of the penetration of tissue from *Chromodoris zebra* show that a determining factor in penetration involves the establishment of a critical H-ion concentration (near 3.5) in relation to superficial cell proteins. The rapidity with which this state is produced depends upon acid strength, and upon some property of the acid influencing the speed of absorption; hence it is necessary to compare acids within groups of chemical relationship. The actual speed of penetration observed with any acid is dependent upon 2 influences: preliminary chemical combination with the outer protoplasm, followed by diffusion. The variation of the temperature coefficient of penetration velocity with the concentration of acid, and the effect of size (age) of individual providing the tissue sample agree in demonstrating the significant part played by diffusion. In comparing different acids, however, their mode of chemical union with the protoplasm determines the general order of penetrating ability.

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**The Influence of Temperature on the Breaking down of Chlorophyl by Light.**

*L. A. Iwanoff, Biochem. Ztschr., Berlin, 131:140, July 29, 1922.*

The photochemic reactions are dependent only to a slight degree on temperature. The temperature coefficient varies from 1 to 1.2, but

risers in the dark reaction to 2-3. Only on carbonic acid decomposition is the coefficient variable within 0-30° from 2.4 to 1.8. As chlorophyll takes part in this complicated reaction by its decomposition under the influence of light, it was sought to determine the coefficients for this. The disintegration of dissolved chlorophyll under the different conditions of oxidation has, like the other photochemic reactions, a very low temperature coefficient and is therefore, in contrast with photosynthesis, only slightly dependent on temperature. It varies according to the solvent and is higher in collodion than in alcohol or in turpentine, and there are still higher figures for the chlorophyll with which manufactured paper is impregnated according to Eders' method.

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**Absorption of Nutrients and Plant Growth in Relation to Hydrogen-Ion Concentration.**

*Olof Arrhenius, J. Gen. Physiol., 5:81, Sept. 20, 1922.*

The effect of H-ion concentration upon growth has been studied by many workers, including the present author, who reports his methods and results in this paper. The experimental technic was as follows: Into glass jars of 1 gallon capacity (which were covered with black paper and enclosed in white boards) disks of galvanized iron netting ( $\frac{1}{4}$  in. mesh) were placed. The disks were covered with a layer of paraffin and two paraffined wires were fastened on opposite sides of each disk. Seeds were placed in the 100 holes bored equally distant from each other in each disk; 3 liters of the nutrient solution were poured into the jar and the disk was suspended by the wire so that the solution was level with the lower surface of the disk. Then the seeds were covered with filter paper and placed in the dark for germination. After 3 days the filter paper was removed and the cultures left for 1 day in the laboratory and then transferred to the greenhouse. Every day 2 or 3 liters of air free from carbon dioxide were passed through each jar. The reaction of the solution changed considerably and it was therefore necessary to adjust it every day by adding acid (HCl) or alkali (NaOH). The solutions were changed every fortnight and the loss by transpiration measured. During the first period of growth the germinated seeds were counted every day. After 2 weeks the cultures were thinned out, at haphazard, so that every fourth or fifth plant was left. When changing the solution every fortnight the length of tops and roots was measured. At the same time 1 liter of the solution was taken out for analysis. When the experiment was finished the plants were dried and roots and tops weighed separately. As culture solution a Hoagland solution (0.78 atmosphere) was used. After use as nutrient media for a fortnight the solutions were analyzed for K, Ca, Mg, PO, NO<sub>3</sub> and SO<sub>4</sub>. The author's tabulated results show (1) the percentage of seeds germinated, (2) the percentage of seeds living after two months, and (3) the rate of germination. It was found that the absorption of nutrients depends to a large extent on the reaction of the substrate. At maximal growth the intake of salt is at minimum. Different ions are very differently affected. The intake of water was found to be independent of the absorption of

salts, but there was good agreement between growth and the intake of water, probably due in part to the increased transpiration when the leaf surface increases.

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**The Chemical Constituents of Green Plants. XIX. The Presence of Lactic Acid and Succinic Acid in the Leaves of the Raspberry (*Rubus Idaeus*).**

*Hartwig Franzen and Emmi Stern, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:195, Aug. 24, 1922.*

In evaporation of the filtrate of the lead precipitate of aqueous extract of raspberry leaves, abundant amounts of a salt consisting chiefly of magnesium lactate crystallized out. Experiments were made to determine whether there were other acids besides lactic acid. The magnesium salt was washed in water, the acids freed by the addition of sulphuric acid, extracted with ether, the acids that were soluble therein transformed into esters and the esters subjected to fractional distillation in a vacuum. In the filtrate of the magnesium salt many crystals were found on evaporation in a vacuum. The masses of salt consisted mostly of lactic acid salts. The etheric extract obtained from this filtrate was for the most part lactic acid: in addition there were small amounts of a body soluble in benzol, a very little succinic acid and a little unsaturated acid.

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**On a Possible Asymmetry of Aliphatic Diazo-Compounds. III.**

*P. A. Levene and L. A. Mikeska, J. Biol. Chem., 54:101, Sept., 1922.*

Previously the authors reported several observations which seemed to point to the existence of an optically active diazodiethyl succinate. This note contains additional proof in the same direction. Curtius has shown that acting with diazo-ethyl acetate on benzoic acid, benzoyl ethyl glycolate is formed. It was expected that under similar conditions diazodiethyl succinate would form benzoyldiethyl malate. It was also expected that this substance could be prepared free from malic or fumaric esters which may form as by-products, since the former possesses a much higher boiling point. These expectations were realized. Acting with diazodiethyl succinate on benzoic acid, pure benzoyldiethyl malate was obtained. Under similar conditions, diethyl malate acting on benzoic acid did not give even a trace of benzoyldiethyl malate.

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**Imidazoldicarbonic Acid in the Recognition and Separation of Organic Bases.**

*H. Pauly and E. Ludwig, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:165, Aug. 24, 1922.*

In an experiment in the graduated decomposition of imidazoldicarbonic acid, a beautiful crystalline compound was obtained. This was



acid imidazol imidazoldicarbonate. This instigated the preparation of salts of other bases with this acid, and in many cases the acid can be recommended for the recognition and separation of organic bases of different kinds. Decidedly the biimidazates are equal to the expensive gold and platinum chlorid double salts in capacity for crystallization and probably even superior to them in beauty. Imidazol acid, however, has one slight disadvantage: It exceeds formic acid in strength, but in separating diimidazates of very volatile or slightly basic nature from water, there is a slight degree of dissociation with the giving off of a small amount of free acid. Advantages of the diimidazates are their colorlessness, their stability in the case of easily oxidizable bases and the salts formed with oxidizing acids, as well as the fact that they do not give an oily precipitate. Their separation from free acid is readily accomplished, because of the very slight solubility of such acid in water.

There are also basic salts, which in the case of the amines are readily soluble, but practically only the acids are to be considered: plant bases can be distinguished from one another, and with conin, for example, a biimidazate is obtained that is only very slightly soluble in water, in contrast with nicotin. Also in the amino-acids of basic nature called hexone bases considerable differences in the characteristics of the diimidazates are to be distinguished. The acid is a dibasic one, not a monobasic one as was formerly assumed.

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#### Keratin. I.

*A. Heiduschka and E. Komm, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:221, Aug. 24, 1922.*

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The keratins are distinguished from other albuminoids by their firm resistance to peptic and tryptic digestion and their relatively great resistance to acids and alkalis. They are generally affected by the two latter only when these are heated and are wholly or only partially split depending on the concentration of the cleaving substance and other conditions. The cleavage extends to the protein building-stones, the amino-acids, which form the keratin molecule. The authors' experiments attempted to split horny substances by the action of heat alone. If horn is heated at atmospheric pressure it becomes carbonized at 300° C. and the combustion gases have a peculiar odor. On heating in a vacuum a brown distillate is formed and a porous carbon remains in the retort. On heating in a closed space, a cleavage takes place at a temperature dependent on the duration of the heating; very strongly smelling gases develop, sulphureted hydrogen, ammonia and organic sulphur compounds, and a brown viscid liquid with an alkaline reaction. On heating the external and hottest part of the horn, an extensive decomposition takes place with primary or secondary formation of ammonia and water. This may bring about a weakly alkaline hydrolysis. If ammonia (20%) is added previously, the cleavage takes place under pressure at a lower temperature, as it does also when water is added, but not to the same degree.

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**Glucosamin and Heterocyclic Compounds.**

*Hermann Pauly and Ernst Ludwig, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:170, Aug. 24, 1922.*

There was a question as to how histidin could be formed from glucose through the intermediation of the methyl imidazol produced from the latter by zinc ammonium chlorid. Knoop and Windans considered the possibility of a histidin synthesis by oxidation of methyl imidazol and glycocoll, in which, on the one hand, hydrogen from the methyl group in methyl imidazol was removed by oxidation and, on the other hand, hydrogen from the glycocoll. The true significance of the formation of methyl imidazol from glucose lies in the direct demonstration that in the alkaline dehydration of grape sugar, methyl glyoxal appears as the primary cleavage product. But the formation of methyl imidazol does not give any information on the genetic relationship between the hexoses and these hexone bases. Not only imidazol but pyrrol can be obtained more easily from glucosamin than from glucose. With reference to the imidazol group, an imidazon is obtained in the body originating from glucosamin and phenylisocyanate when water is given off, and glucimidazol when isocyanic acid is used in place of phenyl isocyanate. It has not been possible to produce oxyacids in this way; on oxidation only imidazol carbonic acid was produced. When free glucosamin was brought in contact with some dicarbonyl bodies, pyrrol compounds appeared, and also when glucosamin hydrochlorate was heated dry in a test tube with some zinc chlorid. In the dry distillation of bone the formation of pyrrol is to be attributed to the high content of the chondromucoid in combined glucosamin.

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**The Action of Chymosin and Pepsin. VII. Experiments in the Purification of the Gastric Enzyme.**

*Olof Hammarsten, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:241, Aug. 24, 1922.*

From the gastric mucous membrane of the hog a hyaline substance was obtained that acted as an enzyme; this was a mixture of enzyme and a hyaline protein substance and was regarded as crude pepsin. An attempt was made to obtain a pure enzyme by 2 methods. (1) The salt-free acid solution of the hyaline substance was denatured through autodigestion by brief heating to body temperature, or (2) without any denaturizing an attempt was made to produce a pure, highly active enzyme from the hyaline substance. According to Method 1 the solution of crude pepsin in HCl was freed from NaCl and other dialyzable substances by dialysis against acids of the same strength. But the greater part of the pepsin remained in solution and the small amount precipitated was less pure than that remaining in solution. By Method 2 the crude pepsin was subjected to fractional extraction with water. Though a comparatively pure and strong enzyme solution was thus obtained, no enzyme preparation was recovered in solid form. This objection is not important because solutions of enzymes are generally employed. These can be kept for a long time

without losing their strength, and the crude pepsin is easily obtainable. The latter represents an enzyme preparation in a solid form, can be kept for years and finally needs only to be extracted with water. If it is desired to prepare from the crude pepsin a pure salt-free solid enzyme, it is only necessary to desiccate the crude pepsin after washing it in a little water. But this, after a little time, is difficult to dissolve and gives in gastric HCl a less pure and therefore less active solution. But enzyme solutions prepared in this way lack the parallelism between pepsin and chymosin action shown by Pikelharing's pepsin. The latter has greater sensitiveness to OH ions. The crude pepsin is readily obtained if enough hog stomachs are available. It is important for the purity of the crude pepsin that the gastric contents be emptied and the mucous membrane cleaned soon after the animal is killed. Infusions must be absolutely clear, hence the filtrate must be passed through the filter several times. Better results are obtained in the winter than in the autumn. However, good enzyme solutions can be prepared even from crude pepsin that is not absolutely pure.

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**The Action of Chymosin and Pepsin. VIII. Different Sensitiveness of the Gastric Enzymes of Calves and Hogs to the Action of Alkalis.**

*Olof Hammarsten, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:260, Aug. 24, 1922.*

The destruction of pepsin and chymosin by alkalis does not occur proportionately. That this was denied by Michaelis and Rothstein is explained by the fact that different enzymes were used, that from hog stomach by Michaelis and from calf stomach by the author. In the latter there are pepsin and typical chymosin, while in the hog stomach milk coagulation is produced not by typical chymosin but by a substance resembling Bang's parachymosin. This unequal resistance of chymosin and the so-called parachymosin to alkalis is manifested in the neutralization of the natural gastric juice; parachymosin is destroyed with extraordinary rapidity by the slightest alkaline reaction. Calf chymosin is very resistant.

For purposes of comparison, calf and hog enzymes of approximately the same concentration were treated at the same time with the same amount of alkali and, after neutralization, were tested both for pepsin and for chymosin action. The chymosin action of hog stomach was decreased much more by the action of the alkali than that of calf stomach. In the first, it sank on alkalization in 2 minutes to  $\frac{1}{4000}$ , in calf enzyme after 8 minutes to  $\frac{1}{2}$ . The pepsin action was greatly decreased in both cases, and in the hog stomach parallel with the destruction of chymosin action, but not in the calf enzyme. In the hog enzyme it was after 2 minutes  $\frac{1}{4000}$ , in the calf enzyme  $\frac{1}{500}$ . The hog enzyme solution contains much more pepsin and therefore has a stronger digestive action. The proportion was 8:1. But the very fact that the calf enzyme solution was poorer in pepsin and, despite the more prolonged action of the alkali, did not show so great a weakening of pepsin action, indicates that the calf enzyme solution is much

more resistant to alkali than is the hog enzyme. This proves that the stomach of the suckling calf contains 2 enzymes, pepsin and chymosin, while the latter is not found in the stomach of the hog and other adult animals.

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**The Chemical Action of Lab Ferment.**

*G. S. Inichoff, Biochem. Ztschr., Berlin, 131:97, July 29, 1922.*

Hammarsten found that the casein of milk, by the action of lab ferment, is split into 2 kinds of molecules: (1) large ones which under the action of the soluble calcium salts of the milk become insoluble and form a coagulum (paracasein), and (2) small ones which remain in solution (whey albumin). The author's experiments were directed toward preventing the precipitation of the paracasein by the action of lab ferment. This was easily attained by addition of oxalic acid to the albumin solution, which at the same time decreased the hydrogen ions. Calcium salts and lab ferment act in just this way on solutions cooled to below the freezing point. The experiments were made with milk or with casein solutions in lime milk. The active strength of the ferment was determined by an accurately gaged casein solution. The lab ferment does not cause chemical actions in albumin solutions, but physical ones, that is a cleavage of the aggregated condition of the albuminous substances. The formation of paracasein is a purely physical phenomenon; the albumin precipitate is formed by the change in the degree of dispersion in the solution under the action of the ferment in the presence of bivalent metals and hydrogen ions.

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**Study of Emulsin. II.**

*Richard Willstätter and Gertrud Oppenheimer, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:183, Aug. 24, 1922.*

Willstätter and Csanyi take up the question of testing emulsin-containing seed preparations and emulsin preparations by quantitative determination of different sugar and glucosid cleavages to determine whether, for every individual case of hydrolysis there is a specific enzyme. The method of time-value quotients gives a constant relation for the capacity of emulsin to split several substrates in different plant materials and in the comparison of fresh and old materials.

The authors, in order to test enzyme specificity, extended the quantitative analysis of emulsin-containing seeds of *Prunus amygdalus* and *domestica* to some phenolglucosids, to phenylglucosid itself and to salicin, helicin and arbutin. For the hydrolysis of these there was exact constancy of the time-value quotients. Helicin was split the quickest. It is a question of the sugar-splitting enzyme acting on different substrates, not of an action of different enzymes. As a measure for the action of the emulsin the time was determined which is required for 1 mg. of emulsin preparation or plant substance to split off half the theoretic amount of monose from 0.1 gm. water-containing

amygdalin in 20 c.c. at 30° C. and optimal pH. Then the change was found for the comparison of the enzymatic actions throughout with equimolecular amounts of the substrates which give 50% cleavage. Amygdalin, prunasin, methylglucosid, helicin, salicin, phenylglucosid and arbutin were dissolved in the substrates. The hydrolysis of these glucosids was determined by the reduction method of Bertrand. The favorable H-ion concentration was brought about in all cases with acetate mixture according to L. Michaelis' method. In the relation of the time values for the hydrolysis of amygdalin and prunasin compared with helicin, and in the markedly divergent quotients prunase cleavage: amygdalin cleavage, it was confirmed that amygdalase and prunase appear in varying proportions. .

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### The Proteolytic Enzymes of Malt.

*Harry Lundin, Biochem. Ztschr., Berlin, 31:193, Aug. 11, 1922.*

Certain changes appear in the nitrogenous combinations of the barley with albuminous substances during the malting process. A partial solubility and hydrolysis results through the proteolytic enzymes, with the subsequent formation of albumoses, peptones, polypeptids, amino-acids and ammonia. The proteolytic enzymes, of which there are hydrolytic and proteolytic examples, immediately become active at the beginning of the malting process. The author's investigation includes peptases and tryptases in green malt, finished malt and in germinal malt, as well as the behavior of these 3 substances during their autolysis. During the autolysis of green malt with varying H-ion concentration, a pepsin-like enzyme is mainly effective in an acid solution, which splits the highly molecular albuminous substances of the malt into albumoses and peptones, whereas in neutral solutions a trypsin-like or erepsin-like enzyme resolves the split albuminous substances into polypeptids and amino-acids. There are a number of different proteolytic enzymes, such as peptases, tryptases, and less important ereptases and desamidases, in the malt and in the germinal malt. In the autolysis of malt the peptic as well as the tryptic enzymes are well represented, but in autolysis of the germinal malt the latter are especially prominent. To gain a better knowledge of both, enzyme substrates or solutions of enzyme were allowed to react with albuminous substances of different grades of hydrolysis, acid albumin, gelatins and Witte peptone, the H-ion concentration being determined in every case. In malt, a malt peptase splits the soluble albuminous substances of malt and gelatins (but not egg albumin) into albumoses and peptones. For malt, the most favorable concentration is pH 3.7-4.3 and for green malt pH 3.2. In addition, a malt tryptase acts upon neither the highly molecular albuminous substances of malt nor egg albumin, nor gelatins, but splits their peptic products as well as Witte's peptone partly into polypeptids and amino-acids. The most favorable concentration is pH 6.1-6.4. In germinal malt, tryptase splits into polypeptids and amino-acids the soluble albuminous substances of the germ, but not the egg albumin, gelatins and Witte peptone. The most favorable concentration is pH 6.2-6.4. The autolysis in malt and in germinal malt results



from different proteolytic enzymes and occurs only at a H-ion concentration which will allow their simultaneous action.

Peptic malt enzymes were studied by their effect upon thymol gelatin. Neutral salts, which do not change the H-ion concentration, produce only an insignificant effect upon the gelatin-splitting capacity of malt peptase. But hydrogen or hydroxyl ion concentrations are fundamental to the effectiveness of the enzyme. The malt peptase hydrolyzes to albumoses and peptones the albuminous substances of the malt, but not egg albumin and acid albumin produced from it and thymol gelatin. The most favorable concentration for this in green malt is pH 3.2-3.4, and in malt pH 3.7-4.3. The neutral salts have a very insignificant effect upon enzyme activity. Malt peptase occurs as a secretory enzyme. The effective enzyme concentration is much greater in green malt than in malt.

To determine the acidity conditions of the tryptic enzyme of malt, the hydrolysis of Witte peptone at different H-ion concentrations was investigated. Malt tryptase attacks neither the albuminous substances of the malt, nor acid albumin, nor thymol gelatin, but it does attack Witte peptone, although not to complete conversion into amino-acids. The most favorable concentration lies about pH 6.2-6.4 at 37°. The corresponding value for pancreatic trypsin is pH 8, and for yeast tryptase pH 6.9-7.1. Both the gelatin and the peptone method may be used for investigating the germinal malt tryptase. The splitting of gelatin proceeds best at pH 6.3-7.3, the acid limit of pH 6.3 being the same as the most favorable concentration for malt tryptase. The neutral salts at the concentrations used exert a very slight effect upon the peptic and tryptic enzymes in malt and germinal malt, so that the albuminous autolysis runs its course almost uninfluenced.

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#### **The Inactivation of Saccharase by Small Amounts of Silver Salts.**

*H. von Euler and Karl Myrbäck, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121:177, Aug. 24, 1922.*

In the reversible poisoning of saccharase solutions with silver and mercury salts, essential differences have been shown between the phenomena caused by the 2 metals. The toxic action of HgCl was not proportional to its concentration, but in the silver salts there was absolute proportion. Decrease of the amount of enzyme causes no decrease in the degree of intoxication, but rather an increase. The enzyme preparation in the tests had a satisfactory activity, the inversion capacity being  $I f = 84.0$ , the minute value  $\pm 0^\circ = 0.55$  minutes. The optimal acidity was determined by nitric acid and measured electrometrically. In the sucrose solution mixed with the necessary amount of nitric acid, there were 4.8 gm. cane sugar and varying amounts of silver nitrate in 60 c.c. Then the enzyme solution was added. In all experiments the enzyme (1 c.c. solution) gave the inversion constant  $k. 10^4 = 49$ . The concentration curve of the silver poisoning, was strongly dependent on the absolute enzyme concentration.

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**The Activation of an Enzyme Poisoned by Heavy Metal Salts.**

*Robert A. Kehoe, J. Lab. & Clin. Med., 7:736, Sept., 1922.*

The following experiments carried out upon saliva show that this secretion behaves like the inert protein in previous experiments of the author, in that properly chosen neutral salts of the alkali and alkaline earth metals restore it to its normal appearance and activity, after its coagulation and complete inactivation, through the action of heavy metal salts. For the experiments, fresh saliva was obtained by chewing paraffin, the same sample being employed in each series of related observations. A 2% starch paste made in the usual way from a commercial corn starch was used as the substrate. The activity of the enzyme on the starch was tested qualitatively with Fehling's solution, after incubation of the substrate-enzyme mixture in a water bath at 40° C. Quantitative estimations were made with Benedict's solution, the amount of residual blue color being used as an index to the relative quantities of reducing sugars present.

When mercuric chlorid is added to saliva to a final concentration of 0.005 m. a heavy flocculent precipitate is obtained, surmounted by a somewhat opalescent fluid. In the lower concentrations of mercuric chlorid the starch-splitting ferments are inhibited. In any concentration of mercuric chlorid above 0.005 m. they are completely inactivated. Complete coagulation and inactivation require  $\frac{1}{2}$ -1 hour at room temperature, at the end of which time the heavy metal is firmly bound to the material composing the precipitate. At various times (1 hour to 3 months) after mercurial inactivation of saliva, small quantities of it were treated with various concentrations of neutral and alkaline salts of the alkali and alkaline-earth metals. When sufficiently high concentrations of the chlorids, bromids, iodids, and sulphocyanates of ammonium, potassium, sodium, strontium, barium, calcium, and magnesium were employed, most of the precipitate dissolved and the mixture again became a homogeneous opalescent liquid. Simultaneously with the resolution of the precipitate the starch-splitting activity of the mixture was restored. Those salts (nitrates, sulphates, citrates, acetates, and carbonates) which did not resolve the precipitate, did not reactivate the enzyme. These effects were not due to a precipitation of the heavy metal in insoluble form, but to a displacement of the heavy metal from its combination with the material in the saliva, leaving the heavy metal in a soluble diffusible state. The enzyme coagulated and completely inactivated through the effect of mercuric chlorid may thus be restored to 80% of its normal starch-splitting activity.

The same experiments were performed in part with silver nitrate as the inactivating agent. In general, the results were the same as those obtained with mercuric chlorid except that the higher concentrations of the light metal salts were necessary to produce the effects.

The facts as presented indicate the probable protein nature of the enzyme together with the probability of the formation of various compounds of salts with this protein. The practical application of these findings is that the treatment of heavy metal poisoning should be directed to restoring coagulated tissue to its normal state.

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**Attainment of the Second and Third Form of Fermentation by *Saccharomyces Saké*, *Zygosaccharomyces Major* and *Zygosaccharomyces Salsus*.**

*H. Kumagawa, Biochem. Ztschr., Berlin, 131:148, July 29, 1922.*

Under the influence of certain substances with an alkaline reaction, such as secondary alkali sulphites and other basic bodies, variations in alcoholic fermentation occur. In the transformation of fermentable sugar in the presence of sulphuric acid salts considerable amounts of acetaldehyd and glycerin appear in molecular proportions. In contrast with ordinary fermentation which gives CO<sub>2</sub> and alcohol, Neuburg and Reinfurth have called this form of change the second form of fermentation. The other organic and inorganic compounds with an alkaline reaction cause another change in the course of fermentation. Here acetaldehyd develops only temporarily and in the products of fermentation there are mutation products of acetaldehyd, especially acetic acid and ethyl alcohol. This is the third form of fermentation. The author wished to determine whether foreign species of yeasts, such as the Japanese races, would have the same effect as those of German origin and whether it was possible with these other species to carry the variations in fermentation still further. All 3 yeasts named in the title are capable, like German yeasts, of transforming sugar according to the second and third forms of fermentation. The especially resistant *Saccharomyces Saké* gives a larger amount of secondary sodium sulphate than the German varieties tested. The extent, therefore, to which acetaldehyd-glycerin cleavage of sugar takes place is particularly great. The amounts reached 19.65% acetaldehyd and 39.18% glycerin, while the alcohol decreased to 10.12%. The sugar was completely used up under these conditions, and 98.28% of it was found again in the form of the reaction products and carbon dioxid. Theoretically 80.25% of the sugar is transformed in the second form of fermentation. The two Japanese saccharomycetes did not prove superior to the German cultivated yeasts in the capacity for consummating the second form of fermentation. This is due to the fact that both of them have only a weak sugar-cleaving action and leave much of it unaffected. As to the third form of fermentation, *Saccharomyces Saké* proved as capable as the German yeasts. As more alkalizer could be used the extent to which sugar was split into acetic acid and glycerin was somewhat greater.

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**The Influence of Thyroxin on Alcoholic Fermentation.**

*M. Tomita, Biochem. Ztschr., Berlin, 131:175, July 29, 1922.*

Different constituents of the vegetable and animal organism belonging to the group of vitamins have a stimulating action on various functions of metabolism. Among them, however, there are also bodies of a definite chemical nature. For example, the actions of the thyroid and suprarenals are known to be due to thyroxin and adrenalin. The vitamins also promote the process of alcoholic sugar fermentation. Thyroxin has a marked influence on metabolism even in very small quantities. Experiments show that it hastens fermentation.

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**The Breaking up of Meso-Inosite and Glycerin-Like True Sugar by *Bacillus Lactis Aërogenes*.**

*H. Kumagawa, Biochem. Ztschr., Berlin, 131:157, July 29, 1922.*

Natural inosite is a cyclic body of the hydro-aromatic series and has the constitution of an optically inactive hexa-oxyhexahydrobenzol. Certain reactions, however, connect inosite with the true sugars. Furfural can be obtained from it and on its decomposition lactic acid, propionic acid and butyric acid develop. To test its fermentation the author used *Bacillus lactis aërogenes*. The breaking down of the closed-chain inosite is accomplished completely under the action of this bacillus, just as in the open-chain sugars. Hewitt and Stabben have found alcohol and acetic acid, in addition to formic acid, but not acetaldehyd. In the author's experiments acetaldehyd was always present, an important element in the decomposition of inosite. Alcohol and acetic acid are derived from the intermediate product, acetaldehyd. Inosite is a hexavalent, glycerin a trivalent alcohol. The products of decomposition of glycerin with *B. lactis aërogenes* were qualitatively the same; lactic acid and succinic acid were found in considerable amounts and acetaldehyd also when calcium sulphite was added.

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**Study of the Phosphatases. I. Saccharophosphatase.**

*M. Tomita, Biochem. Ztschr., Berlin, 131:161, July 29, 1922.*

The organism has the task of forming phosphoric acid ester in metabolism, which is also observed when the fate of the phosphoproteins is considered. It must be assumed that there are present phosphatases, that is, ferments whose task it is to set free phosphoric acids from organic compounds. These phosphatases have not been studied very much. The author started with sucrose-monophosphoric acid. This was hydrolyzed by a ferment present in the yeast, saccharophosphatase, setting free phosphoric acid, and was also fermented with normal fresh yeast cells. The saccharophosphatase of yeast is active in a neutral, weakly alkaline or weakly acetic acid solution. The animal body also contains saccharophosphatase in the kidney, liver, spleen, pancreas, brain and muscles. These organs are named in the order of their strength of cleavage capacity as determined for equal weights of organs. As in yeast the enzyme is separable from the living cells. Generally sucrose sodium monophosphate was used as a substrate, but the decomposition was also brought about with the soluble calcium salt of this acid. For quantitative determination only the former can be used, in order to avoid the loss of insoluble calcium phosphate. At definite times aliquot parts of the digestive mixtures were removed, coagulated for 10 minutes in a water bath to remove the albumin which had gone into solution in the water, and the clear filtrate was precipitated with magnesia mixture in the cold. After 20 hours the crude ammonium and magnesium phosphate was filtered off, washed and for purification transferred in a nitric acid solution into molybdenum phosphate. The phosphoric acid was then determined. In view of the relations of phosphoric acid to metabolism of the muscle it was

expected that there would be a particularly strong phosphatase action in the muscles, but the experiments showed that the muscles came last. This ferment, which is destroyed by boiling, is designated as an animal saccharophosphatase.

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**Study of the Phosphatases. II. Hexose-Monophosphatase.**

*M. Tomita, Biochem. Ztschr., Berlin, 131:170, July 29, 1922.*

Hexose-monophosphoric acid is capable of alcoholic sugar cleavage; it is obtained by the breaking down of hexose-diphosphate by moderate treatment with dilute acids, preferably oxalic acid, in which one molecule of phosphoric acid is split off. In the experiment, for analytic reasons, the secondary sodium salt was used as a substrate, which is obtained by conversion of barium-hexose-monophosphate with sodium sulphate. The organs of warm and cold blooded animals contain a ferment that hydrolyzes the hexomonophosphoric acid. As with saccharophosphatase, there is cleavage with decreasing strength in the kidneys, spleen, liver and muscles. In solution the salts of hexose-monophosphoric acid are not so stable as saccharophosphatase; when they stand there is a gradual splitting off of inorganic phosphate. It is noteworthy that the kidney has the strongest action, the muscles the weakest. It is conceivable that the catabolism of physiologic lact-acidogen (according to Embden), if the latter is nearly identical with hexose-diphosphate, occurs in stages, like many enzyme reactions. In this the stage of a hexose-monophosphoric acid could also be passed through. But the examinations of organs did not show any preferred position for the cleavage strength of the musculature in comparison with the other organs. The hydrolysis of sugar-phosphoric acid combinations by organ ferments of warm and cold blooded animals in hexose-monophosphoric acid is stronger than in saccharomonophosphoric acid. Probably there are different, though very similar, phosphatases.

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**Crystallized Salts of Some Physiologically Important Sugar-Phosphoric Acid Combinations.**

*C. Neuberg and O. Dalmer, Biochem. Ztschr., Berlin, 131:188, July 29, 1922.*

The phosphoric acid esters of the sugars are to be considered from a physiologic point of view. Biochemically a hexose-diphosphoric acid is developed in the digestion of alkali phosphates and fermentable C<sub>6</sub> sugars with dry yeast or its liquid, with the giving off of water. By partial hydrolysis Neuberg catabolized the hexose diphosphate to a hexose-monophosphoric acid ester. Amorphous salts of both the diphosphate and the monophosphate are pure on analysis. The ordinary phenylhydrazin compound of the diphosphate crystallizes; it no longer contains the unchanged twofold phosphorized molecule of the original sugar, but is derived from the monophosphoric acid ester of an osone. As the hexose-monophosphoric and diphosphoric acid, as



substrates in fermentation, are both important in studies of the phosphatases, it was of interest to prepare crystallized pure salts of the not very stable acids, from which the diphosphoric acid ester and the monophosphoric acid ester could be obtained again in a simple way as unchanged fundamental bodies. This was possible by the preparation of different alkaloid salts which crystallize beautifully and are completely uniform. Strychnin hexose-monophosphate was prepared by the treatment of strychnin sulphate and barium hexose-monophosphate, which crystallizes in needles or prisms, while because of a pronounced sediment at 115°-120° it cannot be said to have a true melting point; on further heating it becomes yellow and at 150° brown and foamy. Brucin hexose-monophosphate was also prepared. Its well developed crystals behave much like those of the strychnin salt, but it is more readily soluble in pure water. A cinchonidin salt was prepared in a similar way. Finally, strychnin hexose-diphosphate was obtained by transformation of the corresponding (slightly soluble) amorphous barium salt with strychnin sulphate and strychnin sucrose-monophosphate, and the transformation of calcium saccharophosphate with equivalent amounts of strychnin and oxalic acid.

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#### The Structure of Fucose.

*E. P. Clark, J. Biol. Chem., 54:65, Sept., 1922.*

An improved method for the preparation of fucose is described as follows: About 10 kilos of seaweed, sufficiently air-dried to become brittle, are coarsely ground in a meat chopper. The ground material is then treated at room temperature for 2 days with 3% HCl (3 liters to each kilo), after which it is repeatedly washed with water by decantation until the washings are no longer acid to litmus. The residue is pressed out and dried. Then 1 kilo of the dried substance is added to 8 liters of boiling 2% H<sub>2</sub>SO<sub>4</sub> and simmered for 3 hours. The undissolved material is filtered upon large Buchner funnels and thoroughly washed. H<sub>2</sub>SO<sub>4</sub> in the filtrate and washings is neutralized with a paste of precipitated barium carbonate. The resulting barium sulphate is removed by filtering through a thin layer of decolorizing carbon on moistened filter paper in a Buchner funnel. The filtrate is treated with basic lead acetate until no further precipitate is formed. The solution is freed from lead precipitate and excess of lead in the filtrate is removed by cautious addition of dilute H<sub>2</sub>SO<sub>4</sub>. After removal of the lead sulphate the solution is evaporated under diminished pressure to about 175 c.c. of syrup. This syrup is dissolved in an equal volume of methyl alcohol by warming on a water bath and sufficient ethyl alcohol is added to make 2 liters. The precipitate is filtered upon decolorizing carbon, and the filtrate evaporated to 150 c.c. The syrup is washed from the flask with small portions of absolute alcohol by warming, and, when all is removed, sufficient absolute alcohol is added to make 450 c.c. Then 75 gm. phenylhydrazin is added and the mixture is placed in an ice-box over night to crystallize completely. The hydrazone is filtered and washed, first with absolute alcohol and finally with ether. The yield is 100 gm. To obtain the sugar, the hydrazone thus

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prepared is sufficiently pure. Of the material 75 gm. is suspended in 1800 c.c. water at about 90° C. and 36 gm. benzaldehyd is added while the mixture is rapidly stirred. The stirring is continued for  $\frac{1}{2}$ - $\frac{3}{4}$  hour. It is advantageous to have an atmosphere of CO<sub>2</sub> in the flask to prevent the benzaldehyd from becoming oxidized. After removing the benzaldehyd phenylhydrazone, the filtrate is treated with carbon. The fucose solution is concentrated to a thick syrup and dissolved in 800 c.c. absolute alcohol (hot). As some impurities are thrown out by this, the solution is filtered, and then concentrated to about 50 c.c. This syrup is removed to a beaker and the flask washed out with small portions of absolute alcohol by warming, 50 c.c. in all being used for this. The sugar begins to crystallize almost at once, and crystallization is completed over night in an ice-box. It is freed from mother liquor, washed with absolute alcohol and ether, and dried. The yield is 38-40 gm. The author prepared from fucose the methyl tetronic acid lactone, and from its optical properties the position of the hydroxyl group on carbon atom 5 of fucose was determined, thus giving the complete structure of fucose. The amids of the methyl tetronic acid and fuconic acid were also prepared, and from a study of their optical properties, together with those of fuconic lactone, the positions of the hydroxyl groups on carbon atoms 2, 3, and 4 of fucose, heretofore determined by purely chemical means, were verified.

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**A Biosynthetic Carbon Chain Compound in the Aliphatic Series.**

*Julius Hirsch, Biochem. Ztschr., Berlin, 131:178, July 29, 1922.*

In the alcoholic splitting of sugar in the presence of bitter almond oil, an optically active ketone alcohol is formed which from its composition must be due to the combining of a molecule of benzaldehyd with a molecule of the acetaldehyd that appears as an intermediate product in fermentation. This is the first example of a real enzymatic synthesis of carbon chains with several members. From the irreversible combination of two aldehyds that do not react voluntarily with each other a long carbon series developed by fermentation. The enzymatic agent that was active in this process was named carboligase by Neuberg and Hirsch. The ketol is 1-phenylacetylcarbinol. The substances with purely aliphatic carbon chains, such as the sugars and their derivatives, the fatty acids and certain amino-acids have an especially important place among the carbon compounds of living nature. The subject of research was to determine whether with the aid of carboligase the synthesis of acyclic ketone alcohols could be carried out with 2 aliphatic aldehyds. This was attempted first with isovaleraldehyd and acetaldehyd; heretofore it had not been possible to bring about a combination of benzaldehyd with prepared acetaldehyd by living yeast cells or cell-free enzyme material. The chain is formed only when the acetaldehyd enters into the reaction as an immediate product of decomposition of a zymatic or carboxylatic cleavage of sugar or pyrrolic acid. If isovaleraldehyd is added to a fermenting sugar solution, more than 80% is converted into amyl alcohol. The necessary

hydrogen is taken from the split sugar molecule. A pronounced carbolic transformation of the isovaleraldehyd would be expected if the hydrating effect of the phytochemic reduction could be excluded, and for this reason the nascent acetaldehyd of the pyrrolic acid was used as a biologic mother substance instead of sugar. The pyrrolic acid seems to be a product of oxidation and cannot furnish any hydrogen in the fermentation. The purely aliphatic acetylmethylcarbinol has already been met with as the natural product of metabolism of different bacteria. The demonstration of acetone alcohol in bacterial transformations and the appearance of small amounts of butylenglycol in culture experiments with *Bacillus lactis aërogenes* in peptone solutions containing acetaldehyd leads Neuberg to consider a hypothetical acyloin condensation among the possible conversions of the acetaldehyd that appear during physiologic catabolism of sugar. This is the function of the carbolic ferment discovered in the yeast cell. The finding of this ketone alcohol in the biologically and chemically clear process of pyrrolic acid fermentation gives a definite proof of a formal biosynthesis of 2 molecules of acetaldehyd and is also the first example of the fermentative formation of a purely aliphatic carbon chain of several members. In the fermentation of pyrrolic acid the finding of acetylmethylcarbinol is of importance because it fills to a great extent a gap which has hitherto existed in the quantitative analysis. In the first balance experiments of Neuberg and Karczag on the decomposition of pyrrolic acid by yeast, only 50% of the expected amount of acetaldehyd was found. A considerable part of this deficit may be attributed to the combining of the acetaldehyd into a compound richer in carbon. At any rate there is a concurrence in the time of cleavage of the pyrrolic acid and of the biologic building up of this compound.

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#### **Unsaturated Fatty Acids of Brain Cephalins.**

*P. A. Levene and Ida P. Rolf, J. Biol. Chem., 54:91, Sept., 1922.*

In the preparation of cephalin, ox brains were extracted first with acetone and subsequently with ether containing 5% water. From the concentrated ethereal extract, the bulk of the cerebrosids was removed by filtration at 0° C. The filtrate was then fractionated with alcohol. The precipitate after purification yielded material which contained all of its nitrogen as amino-nitrogen. Two methods of purification were employed on each sample.

Following the course of analysis as employed in the work on lecithin, the authors isolated from cephalin 2 unsaturated fatty acids: oleic and arachidonic acid. The oleic acid was separated first as a barium salt (mixed with the saturated acids). This was then converted into the free acid and as such was identified by the iodine number and by the stearic acid yielded on hydrogenation. The presence of arachidonic acid was demonstrated by the isolation of its octabromid, and by the isolation of arachidic acid from the product of hydrogenation of the unsaturated fatty acids. A detailed analysis of the chemical composition of these fatty acids is given in tabular form.

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**Unsaturated Fatty Acids of Brain Lecithins.**

*P. A. Levene and Ida P. Rolf, J. Biol. Chem., 54:99, Sept., 1922.*

The present note records the results (in tabulated form) of the authors' analysis of brain lecithins as regards the character of their unsaturated fatty acids. It was found that the brain lecithins also contain besides oleic acid, acids with more than one double bond. Of these arachidonic acid was isolated in the form of its octobromo-derivative.

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**New Apparatus for the Analysis of the Carbon Dioxid Content of the Air.**

*Henrik Lundegardh, Biochem. Ztschr., Berlin, 131:109, July 29, 1922.*

In the study of different biologic processes, especially the CO<sub>2</sub> assimilation of green plants and animal respiration, the variations in CO<sub>2</sub> content of the air are important. The author has constructed 2 new apparatuses for measuring this; because of their nonsensitive arrangement, these are also suitable for field work. The apparatuses in current use are those of Petterson, which gives an accuracy of —2.1 to —2.9% CO<sub>2</sub> in the air, that of Pettenkofer, and the flask method of Letts and Blake. An open zinc vessel in the form of a wide beaker, 15 cm. high and 16 cm. in diameter, rests on 3 feet. The rim consists of a massive, finely ground metal ring with an L-shaped cross section. By means of screws a disc of plate glass is pressed airtight against the rim which is first rubbed with vaselin; in this way it resists the slight differences between internal and external pressure. In order to shut out greater variations in pressure a tube rubbed with vaselin is laid around the ring. Laterally, a large tube leads out, with a cork through which a thermometer and conducting tubes pass. The bottom of the vessel is slightly funnel-shaped and the outlet tube passes from the middle of this. The air for the test is admitted by removing the glass disc. The CO<sub>2</sub> is absorbed by baryta solution. Where only small amounts of air are to be analyzed or the air is in motion, an instrument of the glass bell type, which draws in just the amount of air necessary for the analysis, gives good service.

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**Studies of Human Mixed Saliva. I. The Determination of the Hydrogen-Ion Concentration of Human Mixed Saliva.**

*Henry E. Starr, J. Biol. Chem., 54:43, Sept., 1922.*

In the author's experiment herein described the saliva is collected under oil in a clean receiver. Then 1 c.c. is removed by means of a pipet and transferred to a test-tube containing 9 c.c. of freshly boiled distilled water (pH 6.6 to 6.7) and 1 c.c. of 0.01% aqueous solution of dibromothymolsulfonephthalein also under oil. The saliva and diluent are then mixed thoroughly by stirring with the flattened end of a glass rod beneath the level of the supernatant oil layer. After the

diluted saliva is of uniform "virage" throughout, the H-ion concentration is determined by comparison with suitable standards against a milk-glass background. Sørensen's standards of M/15 primary potassium phosphate and secondary sodium phosphate solutions prepared from Merck's chemicals were employed. They covered the range from pH 5.0 to 8.0 at intervals of 0.1 pH. Readings were made to 0.05 pH. The author's work brought out that (a) saliva undergoes a slight increase in pH on dilution up to a proportion of 1:3 or 1:5, when a plateau is reached and maintained at least until the dilution is 1:12; (b) the use of paraffin as an activator is precluded, for in the author's experience it resulted in every instance in an increase in pH of from 0.10 to 0.60 pH; (c) mixed saliva speedily increases in pH when allowed to stand exposed to air at ordinary room temperatures; (d) centrifugation results in loss of CO<sub>2</sub> and an increased pH of the supernatant liquid.

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**Studies of Human Mixed Saliva. II. Variations in the Hydrogen-Ion Concentration of Human Mixed Saliva.**

*Henry E. Starr, J. Biol. Chem., 54:55, Sept., 1922.*

The author's present studies embraced observations on (1) the influence of alveolar CO<sub>2</sub> on salivary pH; (2) the influence of ingestion of large amounts of alkali; (3) the influence of voluntary deep breathing; (4) the diurnal rhythm in salivary pH during fatigue and excitement; (5) the salivary pH of normal subjects and stammerers, and (6) the influence of emotional excitation.

The H-ion concentration of human mixed saliva was found to vary directly with the alveolar CO<sub>2</sub> after the noon meal. It was also found to vary inversely with the pH of the urine after ingestion of large doses of sodium bicarbonate. Vigorous forced breathing in the open air with mouth closed resulted in decreased acidity of the mixed saliva. The [H<sup>+</sup>] of the mixed saliva was found to vary inversely with the degree of energy displayed by an individual, increasing during fatigue and decreasing during emotional excitement. A group of stammerers who were habitually deficient in the use of their lungs and lethargic in behavior, showed a characteristically high salivary [H<sup>+</sup>]. A group of hyperexcitable psychopathic stammerers showed an equally characteristic low salivary [H<sup>+</sup>]. From 228 healthy normal subjects 610 specimens of mixed saliva were collected. The mean, mode, and median practically coincided at about pH 6.60. The author's observations indicate that the [H<sup>+</sup>] of the mixed saliva parallels the alveolar CO<sub>2</sub> and the H<sub>2</sub>CO<sub>3</sub> content of the blood, rather than the [H<sup>+</sup>] of the blood.

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**Oxyhemoglobin and Hematoporphyrin in Human Bile.**

*Walter Robitschek, Ztschr. f. klin. Med., Berlin, 94:331, June 30, 1922.*

In view of the usual absence from normal bile of free hemoglobin or its iron derivatives and oxidation or reduction products, of Stern's



demonstration of hemoglobin in the bile of rabbits under certain conditions, and of Filehne's inability to bring about a corresponding condition in dogs, the author studied the problem in man. Investigations were carried out on patients with a drain in the hepatic duct following occlusion of the common bile-duct. The findings therefore pertain only to hepatic bile. Search for hemoglobin was made spectroscopically. The blood-pigment was thus directly demonstrable as oxyhemoglobin, although in many cases it was necessary to first dilute the bile with distilled water to an optimum concentration. A short time after operation the bile became devoid of hemoglobin, in all 9 cases investigated, and it remained so as long as drainage was continued.

In an attempt to duplicate Stern's experiments on rabbits 4 patients received intravenously physiologic (0.85%) salt solution in quantities of 500 to 800 c.c. The bile was then examined spectroscopically at hourly intervals. Hemoglobin could not be demonstrated in a single instance.

In 3 patients receiving 10 c.c. of 1% salt solution, no hemoglobin appeared in the bile. In 2 of 4 patients receiving larger quantities of a 1.5% of salt solution by intravenous injection, hemoglobin could be demonstrated in the bile. The author explains the action on the basis of the liberation of hemoglobin from red cells "laked" after the introduction of a hypertonic salt solution into the circulation. If such "laking" occurs in excess of the capacity of the liver to transform the hemoglobin into bilirubin, hemoglobin is recovered in the bile.

To demonstrate hematoporphyrin in human bile the author filled the gall-bladders of 14 patients with a mixture of barium chlorid and barium oxid. The resulting precipitate was extracted with alcohol containing hydrochlorid acid. In 3 cases there was a positive reaction for hematoporphyrin, all others remaining persistently negative. The origin of this hematoporphyrin has not been traced definitely, but as hematoporphyrin could not be detected in the blood in any of the positive cases, the conclusion is justified that this pigment, when found in the bile, has been formed in the liver. The finding of hematoporphyrin in the bile is particularly significant when accompanied by the corresponding pigment in feces; hematoporphyrin was demonstrated in the feces of only those patients in whom hematoporphyrinic bile entered the intestine; the feces became literally stained with biliary pigments. In all cases with negative findings for hematoporphyrin in the bile there was no hematoporphyrin in the feces. This lends emphasis to the assumption that fecal hematoporphyrin is formed in the liver.

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#### **The Effect of Bile Salts in the Urine on Routine Tests for Albumin.**

*Symmes F. Oliver, J. Lab. & Clin. Med., 7:743, Sept., 1922.*

The attention of the author was directed to the frequency with which albumin is reported in the urine of patients suffering from various diseases of the liver and biliary passages, particularly those with jaundice of hepatic origin. Often albumin is reported without casts or other evidences of renal disease. Routine urinalysis performed

on a large number of cases of obstructive jaundice revealed that practically all gave positive tests for albumin with the acetic acid and heat tests, Heller's cold nitric acid test, and Robert's reagent. In a few cases a double ring, one just above the other, was obtained with  $\text{HNO}_3$  and with Robert's reagent. These rings formed immediately and became stronger on standing. The occurrence of this double ring suggested that 2 different substances were present in the urine, which reacted with the reagents used. The lower ring exactly at the point of contact of the reagent and urine was found to be albumin. The upper ring was not due to urates. Mucin and various nucleo-albumins may, under certain conditions, give reactions that lead to confusion. If mucin is suspected, dilution of the urine together with filtration would eliminate it as a factor. The ring described in this paper is a broad milky one just above the layer of contact between the reagent and the urine, and tends to diffuse upward rather rapidly, ultimately clouding the entire urinary layer.

Since the urines examined were all obtained from cholemic patients, it seemed logical to assume that certain constituents of the bile might be responsible for these changes. Solutions of bile salts were therefore prepared and tested with the above reagents. In all cases a ring such as described formed just above the layer of contact of the reagent and the solution used. Urines that were known to contain albumin were then treated with traces of bile salts and tested. The double rings were obtained in all specimens examined. The original urines were tested for bile salts and a decided increase in bile salt content was disclosed.

The clinical importance of these findings was demonstrated in 2 cases cited by the author, where it was necessary to determine whether a condition was hepatic in origin or whether the pathology is indicative of renal disease.

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**The Use of the Ninhydrin Reaction in Microscopic Preparations to Demonstrate Low Albumins in the Liver Cells (Stored Albumin), and in the Blood.**

*W. Berg, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:543, Aug. 14, 1922.*

The albuminous nature of the droplets found in the liver cells of well-fed animals (rabbits and cold-blooded animals) could be determined by means of Millon's reagent. The ninhydrin reaction was drawn upon to confirm the suspicion this is a less complex albumin. True albumins can be precipitated from protein mixtures more readily than albumoses and peptones, the latter more easily than polypeptid mixture. Hence microscopic fixation can be so managed as to convert the higher albumins into an irreversible form, while the others remain capable of reacting. Preliminary tests with 5% solutions of Witte peptone and erepton showed that the most suitable fixing agent was formol (10%) or Ciaccio's solution (5% potassium bichromate and 20% formol). By these fixing agents the higher albumin bodies are ruled out and only the lower constituents enter into the inhydrin reaction.

Cubes of the liver of salamanders (each side measuring 2-3 mm.)

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were kept in 50 c.c. of fixing fluid for 18-24 hours, washed in running water  $\frac{1}{2}$ -1 hour, and cut into frozen sections 10-15  $\mu$  thick. The sections were boiled for a minute in a 1:500 ninhydrin solution in a watch crystal and then examined in glycerin. In starving salamanders the parenchyma cells of the liver gave no ninhydrin reaction; their erythrocytes and eosinophil leukocytes gave the same reactions as those of well-fed animals. When 10 c.c. of 2% erepton solution is boiled with 0.5 c.c. of 1% ninhydrin solution for a minute, the resulting dye does not stain the homogeneous albumin droplets in the liver cells of well-fed animals, but does occasionally stain the vacuolated decomposition products of the same. The staining of the blood-cells is independent of the nutritional condition of the animal and conforms with the result of the ninhydrin reaction. Apparently the albuminous drops consist of lower albumins, or they do not contain much albumin. The behavior of human blood-cells was also studied. As in the liver, complete fixation causes the reaction nearly or entirely to disappear. The possibility could not be ruled out that the reacting substances might be derived from the blood plasma and that the dye stained the blood-corpuscles secondarily; yet the reaction is obtained, though more feebly, with isolated fixed and washed erythrocytes. Histochemically, staining with ninhydrin dye is the same as staining with acid dyes.

It has been demonstrated that albumin, in a low form, is stored in the erythrocytes of salamanders, cats, dogs, rabbits and human beings, as well as in the liver cells of salamanders, while it could not be definitely shown in the granules of eosinophil leukocytes.

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**Nitrogen Determination in Cerebrospinal Fluid by Bang's Micro-Kjeldahl Method.**

*P. A. Hoefer and Julie Mannheim, Biochem. Ztschr., Berlin, 131:145, July 29, 1922.*

In the methods hitherto used for albumin determination in the cerebrospinal fluid larger amounts of fluid are necessary than are usually available. The albumin content of the blood serum is over 7%, that of the normal spinal fluid about 0.025%. For the determination of the total nitrogen and the albumin nitrogen in the blood by Bang's method, 20-30 mg. blood are sufficient, and for the determination of rest nitrogen, 100 mg., but for determination in the spinal fluid considerably larger amounts are necessary. About 0.5 c.c. must be used to get harmonizing results. As the torsion scales can only weigh 500 mg. and Bang's paper plates cannot absorb so much, a modification of the method must be made and the amount of spinal fluid measured accurately with pipets. The spinal fluid must be used as fresh as possible in order to avoid sources of error from evaporation or soiling with bacteria. Until used it must be kept in closed glasses (with thymol added) in the refrigerator. After the treatment of the spinal fluid with sulphuric acid and a catalyzer, the ammonia formed is distilled off and the loss of acid is determined iodometrically. The nitrogen determination requires only a few minutes. The lowest value found was 0.17 per thousand in irritation of the labyrinth; diseases of the central nervous system also showed low values. The strength of the

Wassermann reaction and the globulin reaction do not run parallel with the increase in total nitrogen. In cases of tabes with negative Wassermann the spinal fluid values were lower than in Wassermann positive tabes.

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**A Convenient Apparatus for Simultaneous Determination of Total Nonprotein and Urea Nitrogen, and for Prevention of Bumping of Filtrate during Boiling.**

*John Walker Moore and Louise Jones, J. Lab. & Clin. Med., 7:756, Sept., 1922.*

The apparatus herein described has the advantage that the estimation of total nonprotein and urea nitrogen can be carried out successfully by one person in the time allotted for a nonprotein nitrogen determination in the original method. The apparatus is essentially the same as that recommended by Folin, with the addition of glass tubes with deflected capillary points which are inserted into test-tubes. These tubes are connected with rubber to the curved arms of a Y-shaped brass tube, whereas the straight arm of the Y is connected to a protected rubber bag for inflation. In operation, one test-tube is used for the total nonprotein nitrogen, and the other for urea nitrogen determinations. With filtrate in tubes, the rubber bag is inflated and a constant current of air is allowed to escape through the capillary tip. A vigorous air current is not essential, it is therefore necessary to regulate the air stream by use of rubber screw clamps. The flame is applied to each tube by means of a microburner, and the digestion and distillation of filtrates are carried out simultaneously in the time and manner recommended by Folin. The ordinary collapsible drinking cup is a convenient and adequate protection for the flame of the microburner. During the process of digestion, it is not desirable to continue the air current in the nonprotein tube after the filtrate is about half evaporated, nor to have tip of tubing in this test-tube extend farther than within 1.5 cm. of bottom of tube. On the other hand, in the distillation method of determining the urea nitrogen, the capillary tip extends to within 0.5 cm. of bottom of tube; the air current is allowed to continue throughout the test. This procedure not only promotes smooth boiling, but at the same time exerts a pressure which acts as a safeguard against suction that might take place during the determination. Using the method here described, all annoying bumping is absolutely prevented.

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**The Triketohydrindenhydrate (Ninhydrin) Reaction as a Quantitative Colorimetric Method for Determination of the Amino-Acid Nitrogen. Practical Use of the Method.**

*H. Riffart, Biochem. Ztschr., Berlin, 131:78, July 29, 1922.*

Ninhydrin was first used by Ruhemann as a reagent for amino-acids. Abderhalden and Schmidt used the reaction to demonstrate the

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dialyzable protein substances catabolized by ferments. Neuberg found that a typical outcome of the reaction can also be brought about by bodies which have nothing whatever to do with amino-acids. Halle, Löwenstein and Pribram announced that reducing sugar and aliphatic alcohols of neutral reaction and in very high concentrations also produce a blue color, and finally Herzfeld noted the influence of the concentration of the solution on the ninhydrin reaction and utilized this to work out a quantitative spectrophotometric method. The author made experiments to determine the relation of the hydrate to amins and ammonium salts. In solutions which contain no albumin substance and little or no amin the amino-acid content is given exactly. In solutions which have little or no amin, but do contain albumin that can be removed by dialysis, the amino-acid content can be determined with sufficient accuracy by the aid of a dialyzing factor. The ninhydrin method gives particularly good service when (as in the study of albumin decomposition) it is necessary to follow up the amino-acid content consecutively, but when, with the preservation of uniform experimental conditions, comparative values can be utilized in place of absolute values. The use of ultrafiltrates makes an authentic determination of the absolute value of amino-acid nitrogen possible. In solutions containing larger amounts of amins a positive ninhydrin reaction does not give the content in amino-acid nitrogen alone, but the nitrogen content of all the protein split-products that yield a positive ninhydrin reaction. As the sensitiveness of the ninhydrin reaction to the different kinds of amino-combinations varies the results naturally yield only comparative values.

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**The Clinical Usefulness of Van Slyke's Method for Determining the Total Acetone Bodies of the Urine and Blood.**

*W. Lintzel, Münch. med. Wchnschr., 69: 1234, Aug. 25, 1922.*

Van Slyke has described a method for determining acetone and acetic acid in the urine in which by oxidative transformation of oxybutyric acid into acetone and the acetone precipitation of Denigès, these substances can be determined at the same time as total acetone bodies. The determination is made gravimetrically or by titration from the mercury content. In boiling with mercury in sulphuric acid and chromic acid solution, the acetone is precipitated as a mercury-sulphate-chromate combination. The same method makes the determination of acetone and acetic acid possible if no oxidation is brought about by chromic acid and from oxybutyric acid alone if acetic acid and acetone are first driven off by boiling with sulphuric acid. The same method was used by van Slyke and Ritz to determine the acetone bodies in the serum and blood. The control determinations made by the author have shown the usefulness of the method. In several cases of diabetes the course of the acidosis was observed by daily determinations by this method. Several hundred determinations of acetone bodies in the urine and a series of determinations in the serum showed the usefulness of the method in clinical practice.



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**Experiments on the Adsorption of Uric Acid by Animal Charcoal, and on Colloidal Suspensions and Their Combining Properties with Proteins.**

*K. Harpuder, Ztschr. f. d. ges. exper. Med., Berlin, 29:208, Aug. 19, 1922.*

Retention of uric acid particles in coagulated albumin causes errors in determinations of the uric acid content of blood. It is highly improbable that combinations are formed under strictly stochiometric conditions; it is more likely that physical combination results, since many organic electrolytes exert surface action and adsorption is influenced by electric forces.

The author investigated the behavior of uric acid toward various adsorptive substances. Following agitation of the uric acid solution with animal charcoal and subsequent filtration, the filtrate had become totally free from uric acid. This loss could be explained as due to increased adsorption of uric acid on the surface of the animal charcoal and water solution, with consequent diminished uric acid concentration in the solvent (filtrate). It became of interest to ascertain whether the adsorption of uric acid by animal charcoal could be affected by the addition of other substances with or without surface action. Hydrochloric acid caused an intensification of adsorption proportionate to the concentration of the acid solution added; weak or moderate alkaline solutions arrested adsorption, but this reappeared and was uniformly increased after subsequent addition of a strong alkaline solution. This seems to prove, in the first place, that the entire, undissociated molecule of uric acid is adsorbable. The addition of strong alkaline solution enhanced adsorption by the stimulating effect of sodium ions, present in excess. The same was true of nitrates and neutral sulphates. Strongly surface active substances like acetone and amyl alcohol caused disappearance of uric acid from the surface of the mixture with consequent increased concentration in the deeper portions of the solution. Ethyl urethane proved less effective; methyl and ethyl alcohol and urea had no effect at all. In the latter mixtures the addition of acid increased adsorption, the addition of an alkali diminished or stopped it, while neutral salts caused a mild intensification of the process. Solutions of uric acid, mixed with surface active substances but containing no charcoal, behaved like ordinary aqueous solutions of uric acid.

In experiments on colloid suspensions electric energy played a preponderant rôle. Iron oxid, purified by 3 days' dialysis in distilled water, served as the positive colloid, and an alcoholic solution of mastic, diluted with 9 times its volume of water, as the negative colloid. Colloidal iron oxid adsorbed uric acid, this property being only slightly interfered with by the addition of surface active substances. The mastic solution did not show interaction with uric acid.

Of the various proteins, Hammarsten's purified casein was selected for experimentation. Casein, an amphoteric electrolyte, does not combine as an anion but as a cation, so that there is no separation of the compound by ultrafiltration. The concentration of the uric acid solution exerts a great influence on the degree of interreaction, the latter, in

contrast to true adsorption reactions, increasing both absolutely and relatively with the concentration of the solution up to a certain point. Chlorids, at least in weak solution, exerted no appreciable effect, and neither did surface active but nonelectrolytic substances like acetone and urethane. Acid solutions of casein became cloudy during the addition of neutral uric acid solutions, but the precipitate disappeared on shaking the mixture; alkaline solutions of casein did not become cloudy. This would point to the possibility of a lowering of the stability of casein by uric acid. In the uric acid and casein mixture the flocculation was about 30 points less than in pure casein solution. The flocculation of casein chlorid is readily brought about by neutral salts following the addition of uric acid. Even uric acid alone, in acid solution, causes precipitation of casein.

Serum globulin exhibited identical properties with casein. Globulin combines with uric acid only as a cation, no such combination occurring between uric acid and globulin in an iso-electric reaction. As to the stability of globulin, the changes occurring in consequence of coagulation by heat are less pronounced. The albumins reacted differently, showing no interreaction in alkaline or iso-electric mediums and only moderate union in acid reactions. Of tissue extracts, the products of cattle tissues are able to fix uric acid in considerable proportion under certain conditions. The active substances appear to be moderately soluble in water, more soluble in hydrochloric acid, insoluble in alkalis; they are therefore not simple proteins. Muscle extracts exhibited distinct combining powers, and liver extracts proved even more active; cartilage, however, displayed no such action, which was expected in view of the uricolytic properties of this tissue. Human organ extracts exhibited very slight combining power.

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### **An Easy Method of Obtaining Samples of Urine from the Male Dog.**

*Frank C. Mann, J. Lab. & Clin. Med., 7:760, Sept., 1922.*

The animal is kept in a cage, since there is then a greater tendency to allow the urine to collect in the bladder. A Hoffman screw clamp is placed on the prepuce in a manner that will just prevent the escape of urine. To obtain the specimen in the average animal he is removed from the cage and given his freedom, preferably in the run where he takes his daily exercise. Usually within a very short time he will urinate into the sheath of the penis. By gently loosening the screw clamp the urine can be collected in a container. Specimens can thus be obtained at 1-2 hour intervals. If it is desired to drain the bladder constantly, a ureteral catheter which is easily passed in the male dog, is inserted so that one end lies in the bladder and the other end in the cavity of the sheath, the screw clamp is then applied to the prepuce. Urine will drain from the bladder through the ureteral catheter into the cavity of the sheath practically as fast as it is secreted, from which it can be drained every hour or two.

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**A Convenient Form of Test-Tube Rack.**

*Sterne Morse, J. Lab. & Clin. Med., 7:753, Sept., 1922.*

Test-tube racks in use have one practical disadvantage which is to a large extent overcome in the rack designed by the author. This is the necessity of removing a tube under examination in order that the whole of its contents, sediments, as well as supernatant fluids may be thoroughly observed. The type of rack here figured, in which the tubes are supported by a wire coil, is so constructed, that every part, including the bottom of the tube, can be thoroughly inspected without touching the tube. It also has the merits of lightness, cheapness and ruggedness.

**1c. PHARMACOLOGY AND TOXICOLOGY**

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**Dynamics of the Mammalian Heart under the Influence of Substances of the Digitalis Group.**

*U. G. Bijlsma and M. J. Roessingh, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:235, Aug. 11, 1922.*

The experiments were on isolated heart and lung circulation of cats: The minute volume was measured by Condon's instrument for measuring the rate of blood current in connection with a heart plethysmograph, the heart volume with a Hürthle's piston recorder, the ventricular pressure with a Frank-Peter's spring manometer. The heart-lung specimen was perfused with 200-300 c.c. defibrinated blood, to which 0.03 mg. strophanthin was added per 100 c.c. liquid.

Results: (1) Influence on minute volume: The experiments were varied in such a way that either the venous supply was increased or with a constant venous supply the arterial resistance was increased. It was found: (a) that the strophanthin increased the minute volume, even when the heart previously could not handle the amount of blood supplied; (b) that the strophanthin can keep up a minute volume against a higher pressure when, before the addition of the strophanthin, the venous supply could not be ejected at this pressure. (2) Influence of strophanthin on heart volume: At first the resistance and the supply were not varied in the heart volume examined before and after strophanthin. In these experiments there was a decrease in heart volume after strophanthin. If the resistance was increased to a certain degree, the dilatation of the heart was less after strophanthin than without strophanthin. Similarly with increase in the blood supply, the physiologic limit of dilatation was attained later after strophanthin than without strophanthin. When measurements were made of the diastolic heart volume at which rapid dilatation and decrease of the minute volume began, the so-called diastolic limiting volume, it was found that strophanthin did not markedly change the limiting volume from the normal. (3) Time of expulsion: By comparing the volume curve before and after strophanthin, it was found that after strophanthin quicker expulsion takes place. (4) Influence of strophanthin on the ventricle pressure curve: (a) the contraction is considerably shortened

by strophanthin; (b) the maximum systolic ventricular pressure increases after strophanthin; (c) a heart insufficiency which causes the rising minimal diastolic ventricular pressure can be overcome by strophanthin, by which the diastolic pressure is lowered to 0. (5) The absolute strength: This is measured by the isometric contraction on complete compression of the aorta. In 3 experiments an increase of this strength was demonstrated; therefore strophanthin increases the absolute strength of the heart. (6) Influence on irregularities of the heart: Alternating heart disappears after strophanthin, once heart block is overcome.

The conclusion is that the therapeutic action of strophanthin, like that of adrenalin, is due to a change in the physiologic characteristics of heart muscle, by which the same mechanical effect is obtained with less initial length. This brings about a decrease in the heart volume, by which the heart is removed further from its physiologic limits of dilatation.

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**The Action of Digitalis, Calcium and Barium on Strips of Heart Muscle (Löwe) and the Antagonistic Action of Cocain, Magnesium and Potassium.**

*Martin Braun, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:222, Aug. 11, 1922.*

Experiments were made on circular strips which were taken from the middle of the ventricle of the heart of *Rana temporaria*, without the ganglion cells of the atrioventricular zone. The strips were suspended on wires in the Ringer's solution effervescing with  $O_2$ ; results, written on a kymograph with a light two-armed lever, were: (1) Digitoxin 0.75 gm. to 50 c.c. suspension fluid caused increase of tonus (contraction also without the stimulus of extension), which was overcome by cocain (1:5000), KCl (1:500) and magnesium salt. (2) The same results were obtained with strophanthin. (3)  $BaCl_2$  (1:500) also causes a shortening and rise of tonus which is overcome by  $MgCl_2$ . Cocain works tonolytically only in high concentrations which paralyze the musculature. (4)  $CaCl_2$  (1:10,000) increases tonus like digitalis. The contractions can also be overcome by cocain, and magnesium and potassium salts. Conclusions from the experiments were: Digitalis, calcium and salts of magnesium and potassium act on the same place, that is, as no ganglion cells exist, peripherally from the nerve endings and centrally from the true muscle substance. The point of attack of barium is peripherally from that of cocain at a point which is accessible to magnesium salts.

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**The Elimination of Poisonous Effects upon the Heart by Means of Calcium and Other Bivalent Cations.**

*Ernst Wiechmann, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:588, Aug. 14, 1922.*

Since Loeb's investigations were published, it has been shown that cations may displace one another, or may maintain an antagonistic

relationship to one another. Recently, Zondek has assumed a physico-chemic basis for the action of quinin and arsenic, and of calcium and potassium upon the heart, as well. To further elucidate these facts, the influence of polyvalent cations on the cardiac paralysis due to quinin was studied on spontaneously beating, opened hearts of *Rana temporaria*, Amsler's method. The effects of Ca, Ba, Sr, Mg, Co, Ni, Mn and hexammonocobalt chlorid were studied. The heart paralyzed by quinidin was subjected to the same influences, likewise the heart paralyzed by sodium arsenite. In addition, experiments were made on the effects of the digitalis glucosids upon the heart paralyzed by quinidin. It could be shown that the nature of cation action is characterized by 2 factors: (1) their specifically chemical character and (2) their physical properties. Sometimes the one and sometimes the other component predominates. It developed that only the alkaline earths are capable of acting as antagonists to the injurious cardiac effects of arsenic and quinin. Since other polyvalent cations fail in this respect, this antagonistic effect probably depends more upon the chemical nature of the compensating ions than upon their physico-chemic character. Possibly the chemical process in the quinin effect, as well as in the antagonistic calcium effect, is brought about through the action of phosphatids. On the basis of an increase in the effect of quinin and arsenic through the addition of hardly effective amounts of potassium, Zondek has assumed an identical action of these 3 substances. But this view is untenable, since an excess of potassium in no instance corresponds to an addition of quinin or arsenic. Moreover, the effect of potassium can be compensated not only by the cations of the alkaline earths, but also by other polyvalent cations. Therefore, the action of quinin, arsenic and potassium are not identical. The cessation of heart action due to quinidin can be remedied by strophanthin and digifolin. Aqueous infusion of digitalis is incapable of producing this effect.

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**Quantitative Studies of the Action of Homologous Quaternary Ammonium Bases.**

*Fritz Külz, Pflüger's Arch. f. d. ges. Physiol., Berlin, 195:623, Aug. 14, 1922.*

The curare and muscarin effects of a series of quaternary ammonium bases were studied, leaving out the first members of the series since experience has shown that they do not usually conform with the law of serial proportions. There were examined tetramethyl (TM), trimethylethyl (TME), trimethylpropyl (TMP), trimethylbutyl (TMB), trimethylamyl (TMA), trimethylheptyl (TMH), trimethyloctyl (TMO), triethylmethyl (TEM), tetra-ethyl (TEE), triethylpropyl (TEP), triethylbutyl (TEB), triethylamyl (TEA), and triethyloctyl (TEO) ammonium iodid.

If the substances are arranged according to their just paralyzing effect upon a frog nerve-muscle preparation, it can be clearly shown that the action increases with the higher side-chain group and that the methyl group distinctly augments the effect. A peculiar curve is obtained when the inhibitory effect upon the heart is studied. (TM: 0.0005-0.00033 n., TME: 0.05-0.02 n., TMP: 0.0033-0.0016 n.,



TMB: 0.00005 n., TMA: 0.00033-0.00025 n.). TMH no longer stimulates, but exerts a paralyzing action upon the vagus, i.e. it acts like atropin. TMO acts in the same manner. The approximate effect of the atropin bases was obtained from the strength of the antagonistic effect against a muscarin base. To neutralize the negative inotropic effect of a 0.00005 n. solution of TMB requires 0.00025-0.0002 n. TEM; 0.00025 n. TEE; 0.0002-0.00016 n. TEP; 0.0001 n. TEB; 0.000025-0.00002 n. TEA, and 0.000016-0.00001 n. TEO. The trimethylalkyl ammonium iodids, up to the heptyl derivative, produce a more or less marked contraction of the skeletal muscles, which is neutralized by TMO and the members of the TE series.

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**The Excretion of Alkaloids through the Gastric Mucous Membrane and the Salivary Glands after Subcutaneous Administration.**

*Jakob Karl Huber, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:327, Aug. 11, 1922.*

The author reports his experiments on dogs regarding the excretion of certain alkaloids, in which the drugs were injected subcutaneously. Before the injections a stomach sound was introduced, the stomach emptied and 50 gm. lukewarm water passed into it. After varying intervals of time the stomach was again pumped out and the fluid examined for the drug in question.

**Results.**—Atropin: On injections of 0.04-0.5 gm. atropin in the dog (weight 8 kg.), at no time during the toxic action was atropin present in demonstrable amounts (more than 0.001 mg.) in the stomach and saliva. Acreolin: On injections of 1-5 mg. in the dog (weight 1 kg.), acreolin was not excreted either in the stomach or saliva. After administration of a lethal dose, very little appeared in the saliva or gastric juice—about  $\frac{1}{750}$  of the amount injected. Physostigmin: On injections of 0.01-0.05 gm., a demonstrable amount of the alkaloid did not appear in the stomach or saliva—less than 0.02 mg. Papaverin: On injections of 0.12 gm. papaverin in the form of a 1% solution of the hydrochlorid, and more, the papaverin appeared after 3 minutes in the gastric juice. Veratrin: On injections of less than 5 mg. in dogs of moderate weight (8 kg.), veratrin appeared neither in the stomach nor saliva. It was excreted on the giving of larger doses (5-10 mg.) and was about  $\frac{1}{100}$  of the amount of toxin injected.

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**Effect of Caffein on Accomplishment in Sports.**

*Herbert Herxheimer, Münch. med. Wchnschr., 69:1339, Sept. 15, 1922.*

The action of caffein in increasing muscular activity as shown in ergograph experiments, was tested practically on the amount of work accomplished in running 100 meters. The caffein was given in the form of natrobenzoate by mouth in aqueous solution, 0.25 gm. being given. The time between taking the caffein and performing the work

was 10-15 minutes; 0.25 gm. was chosen as the dose because that is the amount contained in a cup of strong coffee. It was not found that the caffeine increased the amount of work accomplished. This shows that the pure muscle action of caffeine is practically insignificant. A stimulating effect is only to be expected when there is a psychic action.

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**The Mechanism of the Straub Biologic Test for Morphin.**

*W. J. R. Heinekamp, J. Pharmacol. & Exper. Ther., 11:107, Sept., 1922.*

The present series of experiments, made on white mice, indicates that the lordosis, spastic gait and arching of the tail, all of which are due to spastic contraction of the voluntary muscles, are not the result of vesical or anal spasm, whether of peripheral as stated by Macht, or spinal origin, as stated by v. Leersum, but they are due to direct stimulation of the cord; it is not a specific test for morphin since it is produced by other drugs which stimulate the spinal cord. Stimulation or irritation of lower motor neurons gives rise to a spastic condition of the muscles. Since the phenomenon is produced by nicotine, codein, camphor, tetanus toxin, potassium cyanate, strychnin and morphin (drugs which stimulate the spinal cord), and since it occurs after removal of the rectum and bladder, it may be stated that Straub's phenomenon is the result of spinal cord stimulation, and that it is not specific for opium alkaloids.

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**Effects of Pilocarpin on the Blood Picture.**

*H. Zuntz and R. Vogel, Ztschr. f. d. ges. exper. Med., Berlin, 29:159, Aug. 19, 1922.*

Pilocarpin injections cause an increase in vagotonia and a rise in the number of eosinophils, with simultaneous total leukocytosis. The first effect is a rapidly occurring hyperleukocytosis with relative decrease of neutrophils, increase of mononuclears and pronounced eosinophilia. After 2½ hours there are found neutrophilia, hyperleukocytosis and eosinopenia. In dogs, following the injection of 1.1-1.5 mg. of the drug per kilo body weight, there occurs a leukocytosis amounting occasionally to 3 times the white count existing before injection. The polynuclear leukocytes are increased both absolutely and relatively. The lymphocytes, mononuclears and transitionals are inconstant. The eosinophil count may fall in the course of 4 or 5 hours to zero. As in other experiments resulting in increased concentration of the blood through loss of fluid, there is a rise in the hemoglobin content, but in these experiments the increased leukocyte count is not parallel to that occurring in desiccation tests.

Experiments in man were made with about one-sixth or one-seventh the dose above mentioned; 15 minutes following injection of the drug the blood-picture change has attained its maximum intensity. There is a slight increase in all leukocytes. The lymphocyte and polynuclear counts are inconstant. The eosinophil count is practically the one existing before injection.

In splenectomized dogs, injections of pilocarpin cause no change in  
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the white cell count. Administration of atropin obviates the effects of pilocarpin completely; an excess of either drug yields a blood picture characteristic of the action of the preponderating drug, and this quite irrespective of the presence or absence of the spleen.

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**The Effect of Phenylchinolin Carbonic Acid (Atophan) upon Leukocytes.**

*E. Starkenstein, Deutsch. med. Wchnschr., Leipsic, 48:1161, Sept. 1, 1922.*

Mendel's observation that the injection of a solution of atophan in hexamethylene tetramin is followed by leukopenia is in itself not sufficient to ascribe this action to atophan, since an injection of hexamethylene tetramin alone produces leukopenia with subsequent leukocytosis.

That atophan does exert an effect upon leukocytes had been shown by previous experiments. The action of atophan (an interference with diapedesis in the frog's mesentery and in the circulating blood) cannot be explained by leukocytolysis, for if this were the case, the increased uric acid production in man would presuppose a corresponding increase in allantoin in mammals. Yet the increased uric acid in man contrasts with a decrease in allantoin in dogs and rabbits after atophan injection. This proves that Mendel's deduction is incorrect and that the increased elimination of uric acid atophan is not caused by the action of atophan upon leukocytes. The paralyzing effect of atophan upon leukocytes explains its action in checking inflammations, but its effect upon the purin economy is not metabolic, but an influence upon elimination of uric acid. These two actions of atophan are entirely independent.

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**Bacteriologic and Chemicophysiologic Tests with O-Oxy-iodosulphonbenzolpyridin (Yatren).**

*Kurt Herzberg, Klin. Wchnschr., Berlin, 1:1830, Sept. 9, 1922.*

**Bacteriologic Tests.**—Two series each of tests with bacterial emulsions and with carriers gave divergent results because the first yatren preparation contained free iodine. These solutions showed retarded bactericidal effect, and higher concentrations were required. Comparison with phenol showed that in its effects on suspensions of earth bacteria, yatren is superior to carbolic acid only after exposure of 5 days (1% solution killed, against a 5% carbolic solution). Both were about equally effective against staphylococci. In tests with serum no difference could be found between yatren solutions containing free iodine and regular yatren solutions. Staphylococcus is killed by a 3% solution of yatren in 2 minutes; growth is inhibited by 0.5% solution when incubated for 24 hours. Hence the lethal dose is higher than in aqueous solutions (3% against 1%). It would be impossible to reach a bactericidal concentration in the organism. In comparison, phenol has a stronger bactericidal action. When serum was added to 0.1-5% solutions of yatren containing free iodine, precipitation resulted, which cleared upon the addition of more serum, but persisted after addition

of physiologic salt solution. The second preparations showed this phenomenon only after the 5% solution had been evaporated to the original amount. The precipitation also disappeared upon the addition of ammonium, sodium and potassium hydrate. Yatren proved unsatisfactory for preservation of agglutinating and precipitating serums.

**Chemicophysiologic Tests.**—The focal reaction of yatren was studied to determine the chemical equivalent of an increased efficiency. In contrast to milk injections, neither fever nor anaphylaxis developed. Like casein, yatren is an irritant substance differing quantitatively from milk. It was sought to determine by quantitative examinations whether a chemical union of these substances takes place in the diseased organism when healing processes begin. Potassium permanganate and sulphuric acid were added to urine containing yatren, and the precipitated manganese oxid was reduced by oxalic acid. The liberated iodine was shaken out with chloroform and titrated with sodium thiosulfate. In healthy subjects, yatren, if administered intravenously, was quantitatively excreted in the urine in 5½-6 hours, and if given by mouth (free iodine), it was chiefly eliminated by the intestinal tract, only a fraction passing out in the urine. In a number of patients with tumors of the adnexa and salpingitis, the injection produced good clinical results, and, as in healthy subjects, the total yatren was eliminated in the urine in 5½-6 hours. This proves that a chemical combination or a decomposition of the molecule does not occur in the diseased organism.

**Discussion.**—In inflammatory conditions the physical influences were primary; the chemical constitution of the ingested substance is of importance only within the limits of the laws of physical chemistry. Probably yatren tends to inhibit fermentative decomposition and retard phagocytosis. Nothing has been found which points to increased adsorption by the diseased areas. Yatren renders serum albumin more readily precipitable, especially in acutely inflamed foci; possibly it also induces alterations of the cell walls. At all events the physical processes are in the foreground when reparative processes in inflammatory foci begin.

**Therapeutic Inference.**—An elaboration of the therapy of irritative substances is not to be expected from the addition and investigation of new preparations, but from a greater knowledge of dosage and the combination of known therapeutic agents. Success is determined by modifying a preparation to suit the indications in individual cases.

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**Comparative Experimental Studies of the Action of Para-Oxyphenylethylamin (Tyramin) and Suprarenin on the Isolated Intestine and Uterus of Different Animals.**

*Karl Hilz, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94: 129, Aug. 11, 1922.*

Suprarenin was used in a dilution of 1:1000, tyramin 1:100 in Ringer's and tyrodel solution. The intestine of the animals was stretched tight and the curves were registered on kymographs. The experiments were: (1) On guinea-pig's intestine: Suprarenin in a dilution of 1:4 million caused inhibition of movement and decrease of tonus; tyramin 1:20,000, rise of tonus and rise of motility. (2) On rabbit's intestine: Action of suprarenin as in Experiment 1; tyramin

caused partial inhibition, but in many cases increase of motility. (3) On cat's intestine: Superarenin as in Experiment 1; tyramin showed the same action. (4) On dog's intestine: Suprarenin and tyramin caused decrease of motility; suprarenin caused at the same time a decrease of tonus, while tyramin caused an increase of tonus.

On the uterus of the pregnant guinea-pig, suprarenin produced an inhibitory and relaxing action, the same as in the virgin cat's uterus, while the pregnant rabbit's uterus was very markedly stimulated, and also, in many experiments, the nonpregnant dog's uterus. Tyramin caused in all the animals a motor and tonic stimulation of the uterus. From these experiments, conclusions were drawn as to the stimulating and inhibiting innervation of the intestine by both sympathetic and autonomous fibers.

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**The Action of Sulphuretted Hydrogen on Frogs, with Special Consideration of the Different Forms of Spasm Produced in Different Kinds of Frogs.**

*Otto Girndt, Arch. f. exper. Path. u. Pharmacol., Leipsic, 94:277, Aug. 11, 1922.*

Summer and winter *Ranae temporariae* were used, and solutions of  $H_2S$ ,  $HNaS$  and  $Na_2S$  were injected subcutaneously into their lymph sacs. Only the  $HS$  ion proved effective and the symptoms of intoxication depended on its dosage. For instance with 0.03-0.04 mg.  $H_2S$  per gram of body weight of *R. temporaria* there is a stiffness of movements with increased excitability but without increased reflex excitability. If the dosage is increased to 0.055 mg.  $H_2S$  per gram, for days or even weeks there is a peculiar permanent tonic spasm without increased reflex excitability. The spasm is distinguished in this way from a tetanic one. It most resembles the spasms after picrotoxin and carbolic acid and may be of medullary origin, as it disappears after cutting the spinal cord below the medulla. If the concentration of  $H_2S$  is increased to 0.06 mg. and over per gram, then the spasm stage does not appear, but the animals show signs of paralysis with fibrillary twitching.

Harnack who experimented with winter *R. esculenta* produced tetanic spasms which lasted for weeks by the action of  $H_2S$  gas. The repetition of his experiments on ice-cooled summer *R. esculenta* with aqueous and gaseous  $H_2S$  gave the same results as the experiments on *R. temporaria*. In only one *R. esculenta* could a moderate increase of reflex be observed, but the spasms were tonic in character. As no winter *R. esculenta* was obtainable, Harnack's experiments could not be repeated and the question of tetanic spasms after  $H_2S$  could not be decided.

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**Tolerance and Acquired Tolerance of the Mesenchyme Cells in Tissue Cultures for Copper Sulphate and Sodium Arsenite.**

*Julius Lane Wilson, Bull. Johns Hopkins Hosp., 33:375, Oct., 1922.*

Both natural and acquired tolerance shown by an organism for toxic substances may be due to neutralization of the toxin by extra-



cellular substances, or by some intracellular mechanism. Unicellular organisms tolerate certain poisons and develop an acquired tolerance or immunity for concentrations above the lethal dose. The author made experiments with ordinary embryonic mesenchyme cells of the chick embryo and inorganic poisons (copper sulphate and sodium arsenite). The effects of the poisons were measured by comparing the percentage of cultures which showed growth or migration, the size of the growth, roughly, and the maximal duration of life with controls, and by comparing the time required to kill cells cultivated in weak solutions with that required to kill cells in controls treated with strong solutions. The first group gave an idea of the natural tolerance; the second of the acquired tolerance. It was found that mesenchyme cells cultivated in weak solutions of copper sulphate and sodium arsenite developed in 2 days an acquired intracellular tolerance for strong doses of these 2 poisons.

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(1c—144)

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**Certain Derivatives of Butylarsin and Butylarsinic Acid.**

*Jules Tiffeneau, Bull. d. sc. pharmacol., Paris, 29:440, Aug-Sept., 1922.*

The author obtained the dichlorid of n-butylarsin and the chlorid of phenylbutylarsin by allowing mercury butyl to react with arsenic trichlorid and phenylarsin dichlorid. By oxidizing the former with nitric acid, n-butylarsinic acid was obtained. Arsenic chlorid, 150 gm., and mercurybutyl, 104 gm., are heated at about 50° C. for an hour. The filtrate is rectified and exhausted in vacuo. The precipitate is heated with excess arsenic chlorid, cooled and treated with dilute HCl, dried and rectified. Butylarsin oxid is prepared by treating butylarsin dichlorid with a solution of sodium or potassium carbonate, exhausting with ether and evaporating. N-butylarsinic acid is obtained as indicated above, or by oxidizing butylarsin oxid with hydrogen peroxid. The acid forms acicular crystals melting at 158° C., soluble in water and alcohol, but insoluble in ether.

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(1c—145)

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**Influence of Arsphenamin and Neo-Arsphenamin on the Epinephrin Content of the Adrenal Glands.**

*Baldwin Lucke, John A. Kolmer and Grayson P. McCouch, J. Pharmacol. & Exper. Ther., 20:153, Sept., 1922.*

The right adrenal glands of rabbits, injected with single doses of arsphenamin and neo-arsphenamin, in 2-5 times the corresponding therapeutic amounts, were assayed for their quantitative epinephrin contents by the biologic method of Elliott. A considerable range of values was obtained, but on the average, the amounts were almost identical with the average of the epinephrin values of control rabbits. The right adrenal glands of rabbits injected with 2-12 therapeutic doses of arsphenamin and neo-arsphenamin gave, on the average, epinephrin values slightly less than those of control rabbits. Of 9

animals receiving multiple injections, only 1 showed a reduction beyond the range of the controls. No striking difference was found between the influence of arsphenamin or neo-arsphenamin, nor did the time of survival after injection appear to play any appreciable rôle. Histologic studies of the corresponding left glands did not show any noticeable and constant alterations of the chromaffin reaction. The lipoids appeared very slightly increased after a single injection, and slightly decreased after multiple injections.

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(1c—146)

(1c—146)

**Quantitative Studies in Chemotherapy. VI. Rate of Excretion of Arsenicals, a Factor Governing Toxicity and Parasiticide Action.**

*Carl Voegtlin and J. W. Thompson, J. Pharmacol. & Exper. Ther., 20:85, Sept., 1922.*

Following the intravenous injection of an arsenical, a considerable variation was found in the rate of excretion of arsenic among different individuals of the same species. This variation was considered as the chief factor responsible for the variation in toxicity and parasiticide action. Different arsenicals were excreted from the body at different rates, the directly toxic trivalent oxid compounds showing the slowest rate, the pentavalent arsenicals the fastest, and the arsenobenzene compounds occupying an intermediate position. The ratio between urinary and fecal excretion of the arsenic of different arsenicals showed great variations. The greater part of the arsenic left the blood plasma soon after the intravenous injection of the drugs. This research revealed an important relation between the rate of excretion, on the one hand, and toxicity and parasiticide action, on the other. This relationship appeared to depend upon the differences in physical properties of the arsenicals studied. Changes in the chemical constitution affected the physical properties, which in turn determined the rate of diffusion and distribution in the body and the path and rate of excretion of the arsenic, thus governing the toxicity for the host and the therapeutic action.

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(1c—147)

(1c—147)

**Quantitative Studies in Chemotherapy. VII. Effect of Ligation of the Ureters or Bile-Duct upon the Toxicity and Trypanocidal Action of Arsenicals.**

*Carl Voegtlin, Helen A. Dyer and Dorothy Wright Miller, J. Pharmacol. & Exper. Ther., 20:129, Sept., 1922.*

Ligation of both ureters increased toxicity and parasiticide action of those arsenicals which normally show a rapid rate of urinary excretion. The toxicity and parasiticide action of arsenicals with a low rate of urinary excretion in normal animals was not appreciably affected by ligation of the ureters. Complete obstruction of the bile-duct increased the parasiticide action of arsphenamin and neo-arsphenamin, but not of atoxyl, and produced only slight changes in the toxicity of neo-arsphenamin.

(1c—148)

(1c—148)

**Chloromethane Sulphonic Acid.**

*René Demars, Bull. d. sc. pharmacol., Paris, 29:425, Aug.-Sept., 1922.*

The formula of this acid is  $\text{Cl.CH}_2\text{SO}_2\text{OH}$ . The author has devised a mode of preparation simpler than Kolbe's. The sodium salt is made by the action of sodium sulphite upon methylene chlorbromid: 12.95 gm. of the latter, and a solution of 25.5 gm. crystallized sodium sulphite containing 7 molecules water of crystallization in 200 c.c. distilled water, are placed in a liter flask. The flask is surmounted by a double-flow condenser, and is heated until the contents boil gently and the droplets of chlorobromid disappear, which requires about 6 hours. The liquid, placed in a porcelain capsule, is then evaporated to dryness on the water-bath. The product is white, of a salty taste and precipitated with silver nitrate. It is treated with 90% cold alcohol. The residue consists of NaBr and sulphates. The NaBr present in the alcoholic liquid is precipitated with silver carbonate, the alcohol being exhausted and its residue redissolved in water. All NaBr being precipitated, the filtrate is evaporated to dryness. The product should contain only sodium carbonate and sodium chloromethane sulphonate, which are completely separated by 5 exhaustions with boiling 95% alcohol.

The sulphite of sodium appeared to contain sulphates. The latter proved so little increased by the reactions that preliminary treatment of the sulphite seems unnecessary. The silver carbonate, not being wholly insoluble, may be treated with a calculated quantity of sulphuric acid. After exhaustion with the boiling alcohol, the converted carbonate remains.

Sodium chloromethane sulphonate is a white, spongy, hygroscopic, light substance, very soluble in water, more soluble in hot than in cold alcohol, from which it may be obtained in white, pearly crystals melting at  $259^\circ \text{C.}$ ; 10.88% of the water of the hydrated salt was lost in vacuo, 10.58% being contained in the monohydrate salt. The barium salt may also be prepared.

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(1c—149)

(1c—149)

**The Pharmacology of Active Vegetable Galenical Preparations.**

*Manuel Alvarez Ude, Siglo méd., Madrid, 70:181, 205, 227, 250, Aug. 19, 26, Sept. 2, 9, 1922.*

Modern pharmaceuticals are standardized by chemical tests on the fresh plant and the final preparation. However, such methods are not always fully satisfactory, since plants contain not single substances, but mixtures. The directions for gravimetric and volumetric tests are not uniform in the various pharmacopeias. Gravimetric methods, while more exact, are more complicated and difficult. They have been recommended wherever applicable, but volumetric processes are nevertheless largely employed. The latter are preferable with single alkaloids, products of well determined molecular weight, or substances whose molecular weights are identical or nearly so. Under other conditions, and with complex substances not containing alkaloids but capable of

saturating acids and thus giving too high volumetric results, the gravimetric methods are best. In all such determinations, the personal error factor is important. The minimal inherent error is greater in gravimetric than in volumetric tests with complex pharmaceuticals. Most procedures described in the various pharmacopeias are sufficiently exact. No one test is generally applicable to complex substances. In the case of opium, the morphin content ranges from 10% to 15%, according to the pharmacopeial method followed. Similar variations occur with other substances. A given process is valid only for plants obtained as described in connection with the process employed. For a universal standard, the sources and processes must correspond and the method must be described minutely. A pharmaceutical type and species should be adopted for each plant, for which a single standard test method should be devised. The standard process should be simple, quick, clear, concise and easily applied under general laboratory conditions. An international medicopharmaceutical union should be organized, of which every member should fulfil the duties required of him. Periodical meetings of such a union could be held.

Physiologic tests take account of the selective action of certain drugs on warm-blooded or cold-blooded test animals. Methods may be based on the minimum lethal dose, effect on the heart, effect on blood pressure, and so on. At present, standardized and perfected physiologic tests are largely lacking. Many factors are not under exact control, such as individual variations in the test animal, and the species employed. Therapeutic coefficients should be expressed rather as test equivalents than as fixed physiologic values. Physiologic tests without chemical examination of the substance are insufficient. They are applicable for trying out new medicinal substances but lack the exactness of chemical determinations. Moreover, they are not practicable in all pharmacologic laboratories. They are of great value in testing drugs whose properties are insufficiently shown by physicochemical methods. Many drugs owe their effects to the proportion between their several constituents. In such cases, pharmacologic values are shown better by physiologic tests. The latter have been accepted by no pharmacopeia except the U. S. P. in which they are generally optional, being obligatory only with Cannabis. In general, biologic methods are more speculative than practical, the technic is delicate and requires special training. If biologic tests are made officinal, they should be made by competent technicians and in adequately equipped laboratories, as with serums and vaccines. Inexact methods and valueless drugs should be eliminated from pharmacopeias. Plant ferments, oxidizing agents, and other vegetable pharmaceuticals constitute a vegetable opotherapy. The efficacy of some plant drugs is due to two substances, the one activating the other. The field for botanic and pharmacologic research is constantly being extended.

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(1c—150)

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**Ipecac in the Treatment of Blackhead in Turkeys.**

*H. W. Graybill, J. Pharmacol. & Exper. Ther., 20:115, Sept., 1922.*

The age of the birds when they became sick ranged from 29 to 62 days; 19 turkeys were treated, of which 9 died and the rest re-

(Sec. 1—Page 850)

covered. Among those that died, as an example, 1 was normally active by the fourth day after treatment. On the fifth and sixth days it was not quite normally active. Then followed a period of 6 days when treatment was discontinued. The bird improved during the first half of this period, and appeared normal. It was not normally active again, and died following treatment at the end of 14 days. Other turkeys receiving similar treatment recovered. It does not seem probable that the treatment could have been injurious, judging from tests on normal turkeys. A mortality rate of approximately 50% would indicate that if ipecac has any value in the treatment of blackhead, it cannot in all probability be very great.

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(1c—151)

(1c—151)

**The Krause Drying Method for the Preparation of Utilizable Drugs. (Digitalis Cold Extract in Dry Form.)**

*G. Pietrkowski, Klin. Wchnschr., Berlin, 1:1890, Sept. 16, 1922.*

The Krause drying method seems to have brought about great advantages in the preparation of cheap drugs; the material to be dried is reduced to a very fine powder by machinery, and these particles are hurled with great rapidity through heated air. The relatively large surface and the great rapidity bring about drying in a fraction of a second; the drying takes place without heating and without oxidative destruction. The active constituents of digitalis leaves, gitalin and digitalein can only be extracted uninjured in cold water and removed quantitatively. Such a cold extract can be transformed in a very short time in the Krause apparatus into a dry powder fine as dust, which preserves the quantity and quality of the cold maceration unchanged and which keeps well. The value of the extract was determined by frog titration.

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(1c—152)

(1c—152)

**The Cultivation of Medicinal Plants.**

*Henry Kraemer, Internat. Clin., 3:165, Sept. 19, 1922.*

Our supply of native plants is becoming reduced and inferior in quality, some species being nearly extinct. It is therefore important that the drug-growing industry should not be allowed to lose the impetus it acquired during the war. Drugs of uniform quality can be obtained only by controlled cultivation from known seed. Placing this industry on a paying basis in the United States is attended by 2 problems: (1) the obtaining of seeds which will germinate quickly and at low temperatures, and which will run through the vegetative period quickly; (2) the acquiring of more accurate information concerning required soil conditions, proper fertilizers, and methods of cultivation. The writer for instance found, in spite of general belief to the contrary, that natural conditions favored the best production. Temperatures as high as 115° F. were not harmful. Digitalis leaves dried on the stalk on wires in drying sheds had an activity twice that of official standards made from leaves artificially dried.



Plants are propagated from seeds, rhizomes and root stocks. Germination from seeds is begun early in the spring under conditions affording protection. Considerable care is entailed. Rhubarb, valerian, poppy, hyoscyamus, gentian and others, were grown from seed. In propagating plants from rhizomes the latter are cut into pieces, each having 1 or 2 buds, and these pieces are planted. As drugs represent different parts of the plant, these are harvested in different ways. Sometimes more than one crop is obtained in a season. Seeds are collected when ripe and threshed out. Fruits are collected by hand when full grown but unripe. Flowers are gathered in bud or when about to open. The leaves and tops of many herbaceous plants, such as henbane, sage, sweet marjoram, thyme and tansy are used. The shoots are cut off and dried. These plants yield 500-1000 lb. per acre. When roots are used, the plants are first allowed to grow for 2-3 years. Curing improves the quality of some drug constituents, such as vanilla, and would probably enhance the value of belladonna, digitalis, and others. Biennial plants may be made to bear fruit in the first summer if started early in the greenhouse. The establishment of perfume extracting plants and the growth of other manufacturing enterprises would naturally supplement the cultivation of medicinal plants and add materially to its lucrative value.

## TOXICOLOGY

(1c—153)

(1c—153)

### Experiments in Detoxication.

*Karl Mayer, Schweiz. med. Wchnschr., Basel, 52:835, Aug. 24, 1922.*

Attempts were made at neutralizing the action of cocain by calcium in excised guinea-pigs' uteri, rabbits' intestines and frogs' hearts, as well as on living frogs and guinea-pigs. An antagonism was demonstrated between cocain and calcium. Calcium greatly decreases the effectiveness of cocain. The author thinks it is at least worth trying to give calcium chlorid in severe cocain intoxication. In such cases 5-10 c.c. of a 10% solution are injected into the vein. In some mild cases of cocain intoxication, he saw subjective symptoms disappear shortly after the injection. In 1 case where there was a pronounced idiosyncrasy against cocain, such as has been recognized in former unpleasant cases, and where after painting the nasal mucous membrane with 2 drops of a 10% solution, headache, dizziness, nausea and tachycardia developed, the author was able to complete the anesthetization of the nasal mucous membrane after the injection of 0.25 gm. calcium chlorid and to cauterize the lupous tissue. The author questions whether this action of the drug and the toxin is to be regarded as an ionic action or whether it is based on a broader foundation.

The detoxication of the organism may be brought about either by a purely chemical or by a physiochemic process. Cocain and calcium interfere with one another mutually because of their precipitating effect. Lecithin is the organic element, the third substance, on which they act in opposite directions. Cocain is a pseudo-antagonist of calcium. Its effectiveness is inhibited by calcium, strengthened by potas-

sium. The mode of action of cocain is, therefore, dependent on the ion balance between calcium and potassium. They inhibit each other, as has been shown experimentally, in their action on lecithin suspensions.

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(1c—154)

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**Carbon Monoxid Intoxication Followed by Polyneuritis and Scapular, Trochanteric and Lumbosacral Scars.**

*A. Florand, P. Nicaud and P. Froment, Bull. et mém. Soc. méd. d. hôp. de Paris, 38:1271, Aug. 3, 1922.*

A woman, aged 57, after recovering consciousness following exposure to the action of carbon monoxid for an unknown period, had incomplete paralysis of the legs, the extensor muscles being chiefly affected. The knee-jerks were absent, and the Achilles reflexes diminished. Sensory disorders were slight. Three days later extensive scars developed in the named regions but healed in a few days. The tension of the cerebrospinal fluid was slightly increased, but there was no marked cellular reaction or hyperalbuminosis. These signs suggest a carbon monoxid polyneuritis, although the possibility of such a pathologic condition has been denied by Claude and Lhermitte on the basis of animal experiments showing the presence of cortical or spinal hemorrhages, but no lesions of the peripheral nerves. Cases of local gangrene due to carbon monoxid are better known.

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(1c—155)

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**The Treatment of Carbon Monoxid Asphyxia by Means of Oxygen + CO<sub>2</sub> Inhalation. A Method for the Rapid Elimination of Carbon Monoxid from the Blood.**

*Yandell Henderson, Howard W. Haggard and Stuart Scott, J.A.M.A., 79:1137, Sept. 30, 1922.*

At a meeting of the Commission on Resuscitation from Carbon Monoxid Asphyxia, the writers were appointed to conduct investigations both in the field and laboratory on the treatment of carbon monoxid asphyxia by the inhalation method. The ineffectiveness of oxygen alone seems to have been due to several causes: there has been no efficient apparatus available; treatment is generally too long delayed to be effective; when the depression of vitality has extended to many hours of coma, oxygen is comparatively useless. In order to determine how far results similar to those on animals might be obtained on men, experiments were performed by the authors on themselves and some of their associates. The subject spent 30-40 minutes in a gassing chamber of 6 cubic meters' capacity, the air of which contained about 0.2% of carbon monoxid. Immediately after coming out of the gassing chamber, he lay down and the therapeutic inhalation was administered for 25-30 minutes.

It was concluded that manual artificial respiration by the prone pressure method should be employed, when respiration has stopped, to start spontaneous breathing. This object may be assisted by administering oxygen + CO<sub>2</sub> simultaneously. Inhalation of oxygen and

5% carbon dioxid by causing a very full ventilation of the lungs, rapidly eliminates carbon monoxid from the blood and thus terminates the condition of asphyxia. This treatment is highly effective, inducing rapid and complete recovery if applied early enough. Until more definite knowledge has been obtained regarding the conditions in the lung, brain and elsewhere subsequent to gassing, and until treatment has been tested experimentally, it is inadvisable to apply any specific treatment in postasphyxial gassing cases. The evidence here reported indicates that oxygen + CO<sub>2</sub> inhalation and rapid elimination of carbon monoxid greatly decreases the liability to nervous and pulmonary asphyxial sequels. The authors have invented a special inhaler for this treatment.

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**The Tannic Acid Method for Quantitative Determination of Carbon Monoxid in the Blood.**

*R. R. Sayers and W. P. Yant, Pub. Health Rep. (U.S.P.H.S.), 37:2433, Oct. 6, 1922.*

For the method described by the authors certain standards are necessary and they are prepared as follows: Using a modified Keidel tube or any other suitable contrivance, 5 c.c. or more of human blood are drawn and kept from clotting by the addition of 0.05 gm. potassium citrate or 0.02 gm. sodium fluorid per 10 c.c. whole blood. The blood thus obtained is divided into approximately equal parts, one of which is immediately diluted 1:10 with distilled water, while the other is saturated with 3-5% carbon monoxid gas, then diluted 1:10 with distilled water. The saturating of blood with CO should be done before diluting with distilled water, so as to minimize the volume of CO gas dissolved in the solution, because the physical solubility is thus limited to the plasma. From these solutions of approximately all oxyhemoglobin and carbon monoxid-hemoglobin, respectively, mixtures are made which total 1 c.c., but vary from 0 to 100% CO-Hb in steps of 10. These are contained in test-tubes of approximately 5/16 inch inside diameter, and of clear, thin glass. To each standard thus prepared is added 1 c.c. of a mixture consisting of equal parts of a strictly fresh solution of 2% pyrogalllic acid and a solution of 2% tannic acid, after which the tube is inverted twice to insure thorough mixing. Immediately after adding the acid, the tube should be sealed. Standards thus prepared develop their full color in 10-15 minutes, and if properly sealed will remain in a suitable condition of permanency for several weeks.

In making an estimation of the CO in the blood of a supposed victim of poisoning, measure into a test-tube of the same size and glass as used for the standards, 1 c.c. of a 0.05% solution of potassium citrate or 0.03% solution of sodium fluorid, depending on the anticoagulant used in preparing the standards. Then make a small puncture wound in the tip of the sterilized finger of the subject and draw up 0.1 c.c. blood with a capillary pipet. Quickly discharge this into the solution in the test-tube, and add 1 c.c. of the mixture of pyrogalllic and tannic acids as previously described. After inverting twice to mix the constituents thoroughly, and allowing to stand 8-10 minutes, a comparison with the standards can be made and the percentage noted.

(1c—157)

(1c—157)

**Biologic Studies of the Head Glands of Nonpoisonous Reptiles.**

*R. Kraus, Münch. med. Wchnschr., 69:1277, Sept. 1, 1922.*

The question of the venoms and the venom glands of nonpoisonous reptiles has heretofore been studied only superficially. The author has studied the venoms of Opisthoglyphae and Aglyphae. By rubbing the upper lip glands with physiologic salt solution he obtained a fluid that killed doves and rabbits within a few minutes on intravenous injection of small amounts (1 c.c. to 0.5 c.c.). These experiments show that nonpoisonous as well as poisonous reptiles have head glands which produce a deadly secretion. These toxins are biologically different from the venoms of the poisonous reptiles. This proves that the classification of reptiles into poisonous and nonpoisonous ones is not scientific, as both of them produce venoms.

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(1c—158)

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**Chronic Arsenical Poisoning.**

*M. Elzas, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:1152, Sept. 9, 1922.*

Studies made in Holland show that about 0.011 mg. arsenic per liter is normally excreted in the urine. However, urinary tests are not conclusive, since, in arsenical poisoning, the kidney may fail to eliminate arsenic. In a case of polyneuritis observed by the author, the diagnosis of arsenical poisoning rested on skin and other symptoms, as well as on the neuritis. The original diagnosis was avitaminosis of the beriberi type. Ebstein's case of symmetrical dermatitis with paralytic symptoms, attributed to an unknown toxic agent probably diphtheric, was probably one of arsenical poisoning. The symptoms were clearly not due to nephritis. In Ebstein's case, the skin lesions were more extensive than in the author's case, and the paralytic symptoms were more like those of postdiphtheric paralysis.

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**Atophan Poisoning.**

*Knud Schroeder, Ugeskr. f. Laeger, Copenhagen, 84:1141, Sept. 7, 1922.*

Since atophan was introduced, in 1908, it has deservedly enjoyed considerable therapeutic popularity, not only in diseases of the joints traceable to uric acid, but also in sciatica, lumbago, neuralgia and the like. It is, however, a dangerous drug; Schroeder has observed 9 cases in which it gave rise to serious symptoms and he refers to 8 cases observed by others than himself. Among the total of 17 cases there were 9 in which an itching urticaria-like eruption was observed, and in 6 cases it was associated with edema. A febrile reaction was observed in 4 cases, albuminuria in 5, general malaise and headache in 2, cardiac disturbances in 2 and gastro-intestinal disturbances in 8. Even with a cautious dosage, symptoms may appear; 0.5 gm. 3 times a day, increasing by 0.5 gm. a day to 0.5 gm. 6 times a day being sufficient

to cause poisoning. This may be due to (1) local irritation of the stomach or intestine, (2) general poisoning by the drug after its absorption or (3) increased excretion of uric acid and its salts. The first explanation is probably the correct one when the drug causes dyspepsia, for this and allied symptoms can be largely avoided by the simultaneous administration of bicarbonate of soda, and by the patient's drinking plenty of water. General poisoning by the drug may, to a certain extent, be avoided by increasing the dosage gradually, and by periodically discontinuing its exhibition for a couple of days at a time. When symptoms of atophan poisoning occur, the drug should at once be discontinued, and the chlorid or lactate of calcium be given, as these calcium compounds have been empirically shown to be beneficial in drug rashes and other exudative conditions. Considering its toxic properties, atophan is hardly suitable for treatment under ambulant conditions, and it ought not to be procurable without a doctor's prescription—as is at present the case in Denmark.

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**Some Attempts to Commit Suicide with Adalin.**

*H. Poulsen, Ugeskr. f. Læger, Copenhagen, 84:1278, Sept. 28, 1922.*

Apparently no case has hitherto been recorded in Denmark of attempted suicide with adalin, probably because this expensive hypnotic, which can be obtained at any chemist's shop, is practically unknown to the public. In the usual dosage of 1-1.5 gm., the drug ensures a satisfactory natural sleep except when the patient is excessively nervous, delirious or suffering from certain mental disorders or severe pain, requiring more effective hypnotics. Several cases of attempted suicide with this drug in Germany show that it can be tolerated in very large doses. In Fromm's case a man took 4.5 gm. with no other effect than deep sleep during a night and a subsequent sensation of having drunk heavily. Kirchberg's case was that of a woman, aged 29, who was admitted to hospital unconscious after having taken 15 gm. on the previous day. The pupils were contracted, the rectal temperature 40° C., the pulse (140) was barely palpable, and the respiration was 40. The urine was normal, reflexes could be elicited, and Babinski's sign could not be demonstrated. The stomach was at once washed out, and the patient ultimately recovered. Sleep in this case lasted 44 hours, but there were no permanent ill effects. Both of Hucher's cases terminated in recovery after 9 gm. had been taken by one woman, and 17-18 gm. by another. Raschkan's patient, a man, slept for 40 hours after taking 3 gm., and he would possibly have died, had he taken the 15 gm. swallowed by Kirchberg's patient. It is evident from these reports that adalin does not suit the purposes of the would-be suicide.

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**A Case of Veronal Poisoning.**

*S. Bloch and L. Deglaude, Paris méd., 12:276, Sept. 23, 1922.*

Following the ingestion of 9.5 gm. veronal, a woman was in a lethargic condition for 72 hours, after which she recovered without any



complications. The presence of the drug was detected in the urine, cerebrospinal fluid and serum. There was no oliguria or albuminuria and nitrogen excretion through the kidneys was normal. This case shows that veronal is only slightly toxic.

## 1d. BACTERIOLOGY AND PARASITOLOGY

(1d—192)

(1d—192)

### **Transparent Milk as a Bacteriologic Medium.**

*J. Howard Brown and Paul E. Howe, J. Bacteriol., 7:511, Sept., 1922.*

In previous unpublished experiments Howe found that the addition of small amounts of various salts renders milk transparent. This fact was utilized for making a bacteriologic transparent milk medium in the following manner: 1 part skim milk was diluted with 2 parts distilled water, to which 0.4% sodium citrate was added. The reaction of the medium was adjusted to pH 6.8, after which it was subjected to fractional sterilization in the Arnold. The resulting medium was water clear without any precipitate. Sodium citrate was found preferable to the oxalate.

Streptococci, anaërobes, and members of the colon typhoid group, when grown in this medium, showed all cultural reactions noted in untreated milk. Some organisms, notably the paratyphoids, produced a milky translucence, which cannot be seen in untreated milk. The authors attribute this reaction to the decomposition of the citrate with liberation of calcium in the ionized state. This reaction can be produced artificially by the addition of a small amount of calcium chlorid to the sterile medium. The advantage of this clear medium is that changes, due to cultural reactions and growth, are more visible than in opaque milk. As long as the acidity remains below pH 5.5, colorimetric H-ion determinations are easily made.

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(1d—193)

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### **Extract of Indian Corn as a Culture Medium. Cultural and Morphologic Modifications of Some Bacterial Stocks in Extracts of Corn.**

*P. L. Fiorani Gallotta, Igiene mod., Genoa, 15:161, June, 1922.*

The method adopted for preparation of the extract of corn is as follows: half filling an ordinary or Erlenmeyer retort with softened corn and adding enough water to just cover the grains; it is well not to fill it too full because swelling of the corn may burst it in the autoclave; corking with single stopper of cotton over which is placed an impermeable cap and sterilizing in the autoclave for a half hour at 120° C., then leaving it at room temperature for 20 days. The greater part of the corn swells and absorbs the water, rendering it necessary at the time of using the extract to add more water up to the original level, to shake it well, and then filter the solution through cotton, trying the

reaction with litmus paper. Since a sediment generally forms, the limpid liquid above the sediment is transported to sterile test tubes with a sterile pipet. It is then left in the thermostat for 48 hours to prevent any possibility of accidental contamination.

For the experiments 4 different kinds of corn were tried: La Plata corn, red American corn, Italian white corn, and Veronese corn. Experiments were tried with the following strains: pseudocholera (transplanted from agar cultures; abundant colonies); cholera (transplanted from cultures of agar, abundant colonies); short streptococci (transplanted from agar cultures). It was concluded that the cultures of the above strains in the aqueous extracts of corn presented abnormal cultural and morphologic phenomena that varied according to the quality of corn used for preparation of the extract. The acidity of the extract did not impede the bacterial development which, on the contrary, was even more marked for some germs, including those that were alkalophilic. The strains used showed for the most part phenomena of spontaneous agglutination or of bacteriolysis. The vitality of the cultures in the extract of corn is shorter than that of the same strains cultivated in ordinary mediums.

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(1d—194)

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**Changes in Nutrient Agar Due to Clarifying with Egg.**

*Luther Thompson, J. Lab. & Clin. Med., 7:758, Sept., 1922.*

In making a standard agar the method of clarifying should be specified. An agar which is egg-cleared is a special or egg agar, because: (1) Egg adds to the agar certain protein compounds in which sulphur is readily available, as for example cystin. The compounds containing sulphur are not restricted to any one of the several proteins found in egg. (2) The reaction of agar is made alkaline by egg white and acid by egg yolk. (3) A fact seemingly of greater significance than those previously mentioned is the addition of glucose to agar from the white of egg. Such a fermentable substance would affect the rate of growth of certain bacteria, both in anaërobic cultures and on aërobic plates.

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(1d—195)

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**The Assimilative Metabolism of Pathogenic Bacteria.**

*H. Braun and C. E. Cahn-Bronner, Biochem. Ztschr., Berlin, 131:226, Aug. 11, 1922. Also Klin. Wchnschr., Berlin, 1:1824, Sept. 9, 1922.*

In order to study bacteria, it is important to assure the most simple and best conditions of nutrition. All strains of paratyphoid bacilli, it is found, behave similarly in some nutritive mediums but show variations in others. This occurred with all verified strains, wherever rapid and profuse growth was possible. Variations were also observable in those capable of reproduction which grew only very slowly and scantily, e.g. in acetic acid or oxalic acid and ammonia mediums, or when a source of carbon was present. Some strains are

less exacting than others and can get along with a smaller supply of energy. Whether Gärtner's bacilli differ from paratyphoid B bacilli in their synthetic ability and whether they can be differentiated in simple cultural mediums may be explained on the basis that the former behave like the more exacting of the latter. In nutritive requirements there is no fundamental difference. Both of the tested gasless paratyphoid B strains behaved like others of the same species in the medium. In the ammonia-assimilating typhoid strains the conditions are similar to those of the paratyphoid B bacillus. Most typhoid strains are unable to assimilate ammonia even when different sources of carbon and more extensive sources of energy may be drawn upon than the lactic acid. There is, accordingly, a marked difference in the capacity between the typhoid and paratyphoid B strains. On the other hand, the common property of assimilating ammonia indicates considerable similarity between the ammonia-assimilating typhoid strains and paratyphoid B bacilli. The ammonia-assimilating typhoid strains are always more exacting than paratyphoid B bacilli; they grow with greater difficulty and more slowly and no reproduction occurs in the simplest mediums. The retarded growth also occurs in certain paratyphoid B strains. There is considerable difference in succinic acid and ammonia medium: paratyphoid B bacteria grow in it, whereas the others do not. Typhoid bacteria, therefore, do not attack the succinic acid and the various carbon combinations are not uniformly available under simple conditions of nutrition. Oxidation plays an important rôle, as the increased supply of oxygen has a great effect upon reproduction. Oxysuccinic acid is poorly utilized by ammonia-assimilating typhoid bacilli but well utilized by paratyphoid B bacilli. There is also a great difference with the amino-acids, except tryptophan, between the ammonia-assimilating and the nonassimilating typhoid strains, whereas the paratyphoid B bacilli and the nonexacting type of typhoid strains resemble each other very closely. Ammonia-assimilating typhoid strains, which resemble the paratyphoid B bacilli in their synthetic properties owing to the capacity for growth in mediums containing ammonia and also behave like paratyphoid B bacilli in litmus whey, must be considered as typhoid bacilli in view of certain physiologic characteristics and their other biologic behavior, especially agglutination. It was experimentally possible to obtain assimilating strains from ammonia-nonassimilating strains and in this way to show the derivation of one type from the other. In a population of typhoid bacteria, some do not assimilate ammonia and others can utilize it. The reversed process, however, of obtaining nonassimilating from ammonia-assimilating strains, succeeded accidentally only once.

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**The Assimilative Metabolism of Pathogenic Bacteria. II.**

*H. Braun and C. E. Cahn-Bronner, Biochem. Ztschr., Berlin, 131:272, Aug. 11, 1922.*

The relationship between metabolism and the need for oxygen is very close. The simpler the nutritive substances and the smaller their number, the greater is the demand for oxygen; the greater the availability of oxygen, the less exacting are the bacteria. Microorganisms

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which possess extensive synthetic capacity under aërobic conditions, become just as exacting under anaërobic conditions as bacteria which cannot support themselves on less simple substances. A synthesis from ammonia with the exclusion of oxygen is impossible; ammonia is the sole source of nitrogen and anaërobiosis cannot be achieved with it when the sources of energy are multiplied or new ones are added to a soil suitable for aërobic growth. A special source of energy and a complicated organic nitrogenous combination must be available simultaneously for life without oxygen. Naturally, the concentration of oxygen found in the air does not provide the best conditions for all bacteria nor for every condition of nutrition. Not only a diminished, but also an increased, supply of oxygen influences the assimilative metabolism. The differences in metabolism should be estimated according to the individual variations, differences in species, and variations within the same strain. Every species has its constant properties, which are traceable either to the presence or the absence of a function; even varying properties may, when the inconstancy is very definite, be characteristic. In this way, the capacity of assimilating ammonia may be absent or present in one and the same species. The dissimilatory properties may also vary, as may be seen in the utilization of various sources of carbon and energy. The demand for energy divides the strains into exacting and nonexacting groups. Even though assimilative and dissimilative functions vary, the other properties show such typical relationships that no question arises as to the membership of one and the same species. This is particularly noticeable in the delicate reaction to specific composition, as in the serologic properties (typhoid). Among the nutritional physiologic properties, those with a varying relationship should be differentiated. The characterization of the species includes all 3 categories. The variations affect only certain properties and this inconstancy is also characteristic to a certain extent. It would be a mistake, however, to assume the transition of one species into another, as this summary is proof of the constancy of the species.

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**The Use of Agar Slants in Detecting Ammonia Production and Its Relation to the Reduction of Nitrates.**

*G. J. Hucker and W. A. Wall, J. Bacteriol., 7:515, Sept., 1922.*

The use of agar slants for testing ammonia production and nitrate reduction is recommended for the reason that many bacteria fail to grow in liquid media. When the organisms were grown on medium containing peptone, the Thomas test was used successfully for the determination of ammonia production. The Sorensen method is recommended for the same test when no peptone or other organic nitrogen is used in making up the medium. In some cases a negative nitrite reaction in a nitrate medium does not indicate failure to reduce nitrate. Some organisms may convert the nitrite, as rapidly as it is formed, either into ammonia or into the protein of their own bodies. An ammonia determination should supply this information. The organisms thus tested should be grown preferably on a synthetic medium, described by the committee on the Descriptive Chart (1920). This medium con-

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tains no nitrogen except nitrate. Sucrose instead of glucose should be used when the Thomas instead of the Nessler test is used to detect ammonia. If the organisms fail to grow in this medium, peptone should also be added. In such a case, a control must be made to make sure that the ammonia is not produced from the peptone. Four out of 60 nitrite negative cultures produced ammonia when grown on this synthetic medium.

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**The Relation between the Fixed and Free Salts of Bacteria.**

*Madeleine Guillemin and W. P. Larson, J. Infect. Dis., 31:349, Oct., 1922.*

That there is a rapid exosmosis of salts from bacterial bodies at death, when suspended in water, had been shown by Green, Minneapolis, and Larson, whose work suggests that some of the salts at least are free within the cell. The present study was made to determine the nature and relation between the free and fixed salts of bacteria, in particular with *B. coli*. The salts which diffuse out of killed bacteria are referred to as free salts, while those which do not diffuse, but are found in the ash, are the fixed salts. It would seem that there are 2 groups of salts, structural salts, which are tied up chemically or form part of the protoplasm, and unbound salts, which perform purely physical functions. The fixed salts seem to remain constant under different conditions of growth, at least for the same organism. The free salts must vary in amount and to some extent in composition, with the concentration and composition of salts in the medium.

Previous to this work, a qualitative analysis had been made of the ash of *B. coli*, which was found to contain Ca, Mg, Na, K, Fe, Cl, SO<sub>4</sub>, and P<sub>2</sub>O<sub>5</sub>. The organisms were grown on meat extract peptone broth with 0.5% NaCl. A dilute suspension was made, and the cells killed by heat. After standing to allow the salts to diffuse out, the organisms were centrifuged out, dried, weighed, and reduced to ash, while the diffusate was evaporated and any organic matter burned off. Ash and diffusate were analyzed quantitatively, and Ca, Mg, Na, K, Fe, Cl, SO<sub>4</sub>, and P<sub>2</sub>O<sub>5</sub> were determined.

It was shown that the amount of free salts is greater than the amount of fixed salts. The 2 groups contain the same constituents, but in different proportions, with the exception of chlorid and iron, which occur only in diffusate and ash, respectively. The total absence of chlorid in the fixed salts and its presence in the free may show that the chlorid is not essential in cell structure, but is used for some other function. The function of iron in the cell is not known. Phosphate is by far the most abundant element, and seems to be the essential element in cell structure. Sodium and potassium are found in the free salts, sodium predominating. The fact that the latter element appears chiefly in the free salts suggests that its action in the cell is physical. The amount of potassium in the diffusate was almost 4 times as large as the amount of sodium in the ash. This shows that potassium is utilized in cell structure. The results can be regarded as established only for *B. coli* cultivated and treated as described in this paper.



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**An Investigation of American Gentian Violets. Report of Committee on Bacteriologic Technic.**

*H. J. Conn, J. Bacteriol., 7: 529, Sept., 1922.*

Gentian violet is a term which does not refer to any definite chemical compound, but rather to a mixture of dyes of a certain group. The only textile dye of this series which, if pure, has a definite chemical formula, is crystal violet, which is hexamethyl pararosanilin. It was found, in the first series of studies of this subject, that crystal violet and methyl violet 6B were fair substitutes for gentian violet in the Gram stain, but that the methyl violets of lower methylations were unsatisfactory. The present investigation was undertaken as a comparative study between methyl violet 6B, crystal violet and gentian violet for use in the Gram stain. The conclusions were drawn from the reports of the collaborators who used the same samples of dye from different manufacturers and employed the same cultures under the same condition and technic. The samples of these 3 dyes produced in this country compare favorably with those of Grüber, and the crystal violet and methyl violet 6B may be substituted for gentian violet.

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**Methods of Pure Culture Study. Report of Committee on Bacteriologic Technic.**

*H. H. Conn, K. N. Atkins, H. J. Brown, F. Eberson, G. E. Harmon, G. J. Hucker, E. W. Tanner and S. A. Waksman, J. Bacteriol., 7: 519, Sept., 1922.*

*Gram Stain.*—Three different procedures are recommended: (1) Ehrlich anilin gentian violet with the technic given in Buchanan's Veterinary Bacteriology; (2) the ammonium oxalate method; (3) that of Atkins. The last 2, though valuable on account of the keeping quality of the solutions, have not been tried out sufficiently to replace the older method. The committee had found crystal violet to be a very satisfactory substitute for gentian violet in all the 3 formulas.

*Fermentation of Sugars, Alcohol and Glucosides.*—The use of solid mediums is recommended whenever possible. Two lots should be prepared—one the regular beef extract agar, the other a peptone-free agar having the following composition:  $\text{NH}_4\text{H}_2\text{PO}_4$  1 gm., KCl 0.2 gm., agar 15 gm., water 1000 c.c. Adjust to pH<sub>7</sub> by the addition of NaOH. To both these mediums are added 1% of fermentable substance to be investigated and 2 c.c. per liter of a saturated aqueous solution of brom cresol purple. The tubes should be inoculated either on the surface alone, like an ordinary agar slant, or partly on the surface and partly in a stab at the base. Temperature should be the optimum for the particular organism. Acid is determined by the yellowing of the indicator; the degree of acidity is denoted by 1-4 plus signs. Cresol red should be used as an indicator for production of alkalinity. The production of gas can be noted by the presence of bubbles and cracks in the agar. When liquid mediums are used the same procedure is observed as to preparation and indicators. If it is preferable

to grow the organisms without the indicator, the culture is tested on the first, third and seventh days. To test for acid, an indicator having a range which covers the reaction of the culture is preferred.

*Reduction of Nitrates.*—The culture is inoculated into nitrate broth and on to slants of nitrate agar. When the culture fails to give a red color with the standard reagents for nitrate (first solution sulphanilic acid-acetic acid; second solution naphthylamin-acetic acid) it does not prove conclusively that there is no reduction of nitrate. A second test for production of ammonia (Thomas test) should be made. The culture should then be grown in a nitrate peptone agar or broth and peptone broth without nitrate (for control) and on the synthetic medium, the formula of which is: Nitrate 1 g  $K_2HPO_4$  0.5 gm.,  $CaCl_2$  0.5 gm., glucose 10 gm., distilled water 1000 c.c.

*Indol Production.*—The committee recommends the testing of the organism in ordinary peptone solution and in trypsinized bouillon of Frieber. Ehrlich reagent (diamethylbenzaldehyd) is regarded as the most satisfactory test for indol. Because it is too expensive for ordinary laboratory routine the committee recommends that all cultures be tested by the Salkowski reagent, then the positive cultures with the Vanilin test, and then those positive to Vanilin with the Ehrlich reagent.

*Production of Hydrogen Sulphid.*—The method used at present is the lead acetate agar method described by Kligler. The standard beef-extract agar is prepared with 30 gm. instead of 5 gm. peptone per liter, with a reaction of pH 7.2—pH 7.6. Five c.c. 0.1% solution of basic lead acetate, previously sterilized, is added to each tube of agar, after it has cooled to 50° C. Hydrogen sulphid causes a blackening or browning of the medium along the line of inoculation after incubation for 18 hours to a few days.

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### **New Micromanipulator and Methods for the Isolation of a Single Bacterium and Manipulation of Living Cells.**

*Robert Chambers, J. Infect. Dis., 31:334, Oct., 1922.*

The method of Barber for the isolation of bacteria by means of mechanically operated pipets has been used with success, especially in the injection and dissection of animal cells. His moist chamber and needles and pipets left nothing to be desired, but the instrument for manipulating the pipets is unsatisfactory. The author has constructed a new instrument which has advantages over Barber's in simplicity of construction, no lost motion through wear and tear, accurate and continuous control over the pipet in any direction under the highest magnification, maintenance of the needle tip in one focal plane while it is moved in any one of three directions, and the existence of adjusting devices to facilitate placing needle or pipet in position.

The construction of the instrument, the setting up and working are detailed in illustrations. The method of securing proper illumination, and the technic of making the moist chamber of Barber and the needles and pipets are also set forth at length. The instrument is being patented.

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**Chambers' Micromanipulator for the Isolation of a Single Bacterium.**

*Morton C. Kahn, J. Infect. Dis., 31:344, Oct., 1922.*

The author, having worked with both Barber's and Chambers' instruments, comments on their relative merits and reviews Barber's isolation method.

Advantages in construction of Chambers' instrument are the absence of parts which loosen by wear and tear, so that great precision may be had in manipulations; the clamping directly to the stage of the microscope, giving greater rigidity; and the smaller size, bringing all manipulations closer to the microscope. Advantages in accessories to Chambers' apparatus are the brass collars to hold pipets; 2 coarse adjustments and 1 fine, for vertical manipulation of pipets; the use of levers on the screws controlling lateral movement, insuring great delicacy of touch; and the fact that the vertical control screw is away from all working parts, close to the fine adjustment of the microscope.

Barber's isolation method consists in placing minute drops of a liquid culture on the under surface of a specially prepared coverslip over a moist chamber by means of the capillary tubes described, until drops are secured which can be seen to contain only 1 organism. Such drops may be removed and the 1 organism cultured.

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**A Note on the Morphology of Bacteria Symbiotic in the Tissues of Higher Organisms.**

*Ivan E. Wallin, J. Bacteriol., 7:471, Sept., 1922.*

In a stage in the morphogenesis of *Bacillus radicola* that is not well known, there appear, under low magnification of the microscope, 3 distinct regions or areas in the root nodule. On examination with oil immersion lens, the 3 areas are found to contain 3 distinct forms of organisms. Each form is more or less limited to a single area. In the part of the nodule next to the plant root, the nodule cells contain the spherical forms, which correspond to the round forms described by Löhmis. The author interprets this part of the nodule to be the older part, and he therefore calls the spherical forms "senile" forms. The "bacteroid" forms of the bacilli were limited to the central portion of the nodule. In what the author interprets as the younger part of the nodule, the bacilli were all of small variety and not as numerous as the other forms. The author advises the use of mitochondrial technic when dealing with symbiotic bacteria, particularly those that have an intracellular relationship; these are just as fragile and delicate as mitochondria.

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**Experimental Measles by Inoculation of Monkeys, Guinea-Pigs and Rabbits with a Green-Producing Diplococcus.**

*Ruth Tunnicliff and Willson B. Moody, J. Infect. Dis., 31:382, Oct., 1922.*

Earlier work done by Tunnicliff had shown that a small, Gram positive diplococcus could be isolated from the blood, eye, nose, throat,

and sputum of patients with measles, during the preëruptive and early eruptive stages. The organisms were small, round or slightly elongated diplococci, bile insoluble, fermenting lactose and salicin, but not mannite or inulin, growing in pairs or short chains in broth, and producing small green colonies on blood agar plates.

A series of monkeys, guinea-pigs, and rabbits were given intratracheal injections of washings from the noses and throats of early measles cases, and were found to be susceptible, giving mild reactions. The same symptoms and lesions could be produced in these animals by use of the green-producing diplococcus, isolated from the blood and respiratory passages of cases of human measles. Rabbits, after successful inoculation with either washings from the noses and throats of measles patients, or the diplococci, had no fresh symptoms when again inoculated with measles virus. The green-producing organisms isolated from the blood or lung of rabbits inoculated with diplococci from measles, caused Koplik spots and exanths in other rabbits, on inoculation.

That the green-producing diplococcus passes through a Berkfeld filter was shown by the growth obtained from the filtrate. It would seem that the green-producing coccus itself caused the reactions obtained, but there was the possibility that this organism possessed the selective power of carrying the virus of measles.

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**The Pathogenic Action of *Bacillus Asthogenes*, Isolated from a Febrile Affection of Unknown Origin and Occurring in Cochin-China.**

*P. Noël Bernard, Bull. soc. de path. exot., Paris, 15: 577, July 12, 1922.*

The author has studied a febrile affection presenting prodromes of headache, lassitude and nervousness. Nervous and gastro-intestinal symptoms predominate. There are fever, myalgia, headache, insomnia, prostration, furred tongue, anorexia and, usually, constipation. Diarrhea sometimes occurs. The temperature usually continues between 38° and 41° for 5 or 6 days, then falling almost to normal in 48 hours. Asthenia persists for several days longer. In grave cases, the limbs cannot support the body and the patellar reflex is diminished. Of 154 blood cultures made from febrile cases in 1921 and 1922, the bacillus asthenogenes constituted 18. Of the 18 cases, 3 were fatal, the bacillus being recovered at autopsy; 1 of the 3 consisted of a mother and still-born infant. The mother's blood contained the bacillus, which was present in pure culture in the infant's liver. The typical lesions present at autopsy consist of hyperemia of the duodenal and jejunal mucosa, enlargement of the mesenteric glands, congestion of the liver, kidneys and suprarenals and dilatation of the heart. In 2 grave cases finally recovering, paralysis and atrophy of the muscles of the limbs occurred.

A similar condition may be produced experimentally in young pigs. The infection is conveyed by food, the bacillus growing freely in the duodenum and small intestine. The intestinal lesions range from hyperemia to necrosis. Entering the circulation, the bacillus

produces adenitis, hepatitis, bronchopneumonia, nephritis and inflammation of the spleen and suprarenals. The bacillus *asthenogenes* is clearly causative. The infection may be termed "asthenomyalgic fever," and suggests beriberi.

Typical lesions were found, and the bacillus isolated, in pigs and monkeys dying naturally from an unknown disease. The bacillus is widely distributed, occurring on fruits, vegetables, rice and bran. It bears spores resisting temperatures around 110°. Cultures grow in water, rice or bran between 100° and 110°. The bacillus is a facultative anaërobe. The clinical resemblance between the affection thus described and beriberi is striking. The cause of the latter has not been positively proved and the possibility of a bacterial origin shou'd not be excluded.

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***Clostridium Putrificum* (B. Putrificus Bienstock), a Distinct Species.**

*George F. Reddish and Leo F. Rettger, J. Bacteriol., 7:505 Sept., 1922.*

The authors do not agree with recent reports of the British Medical Research Committee regarding *C. putrificum*. Contrary to that verdict, the writers in their studies of this organism, find sufficient morphologic, cultural and biochemical differences to set the Bienstock anaërobe apart from the *C. sporogenes*, *C. tertium*, and *C. cochleareous*. The 4 strains in their possession were all long and slender rods, slightly curved, with a terminal round spore. They resemble *C. tetani* morphologically, but differ from it in nonpathogenicity, in proteolytic power, and in that they do not attack carbohydrates. Important points of difference between *C. putrificum* and the other 3 strains are noted: *C. sporogenes* is actively proteolytic and saccharolytic; *C. tertium* is saccharolytic and peptolytic, but not proteolytic; *C. putrificum* is proteolytic but not saccharolytic; *C. cochleareous* is saccharolytic and nonproteolytic.

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**Separation of Toxic and Nontoxic Cells from Cultures of an Anaërobe Isolated from Larvas of the Green Fly.**

*Ida A. Bengston, Pub. Health Rep. (U.S.P.H.S.), 37:2252, Sept. 15, 1922.*

The single cell method of Barber was used to obtain a pure culture of the spore-forming anaërobe recently isolated from larvas of a species of green fly. In a dose of 0.2 c.c., a culture, developed in meat medium from a single colony, was toxic for mice in about 4 hours. A single cell (spore) derived from this culture was nontoxic for mice; of 2 other single cells isolated one was toxic, the other nontoxic. Morphologically all 3 cultures were identical and this fact, in conjunction with the similarity in cultural reactions, indicates the essential cultural identity of the toxic and nontoxic types. The two kinds of cultures have remained true to type with one possible exception which, originally toxic, had become nontoxic 3 months later. The study is of interest in demonstrating that individuals in cultures originally toxic may spon-



taneously lose that property. Successive transplants of nontoxic cultures have invariably proved nontoxic, showing that slight changes in the medium cannot be the cause, and the toxic properties of both types failed to change in passage through fly larvae. The results suggest the possibility of transformation of toxic cultures of other toxin-producing anaërobes, as tetanus and botulism.

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**The Acid Production of *Bacillus Welchii*.**

*Ivan C. Hall and Samuel B. Randall, J. Infect. Dis., 31:326, Oct., 1922.*

Previous studies had shown that *B. welchii*, grown on meat peptone mash medium, gives rise to an increase in the pH, culminating at about 6.1 in 12-24 hours, followed by a gradual decline toward neutrality in about 200 hours. This increase was thought to be due to acid produced in the fermentation of muscle sugar, and the decline to neutralization by ammonia set free from the protein by the organism. There was also an increase in the titratable acidity followed by a decline. These results were secured in mediums to which no carbohydrate had been added, and the present study was made to determine the effect of certain added fermentable sugars on the pH and titratable acidity, and their interpretation with reference to the utility of the peaks of these curves as criteria of freedom from sugar. Meat peptone mash media and media to which 5% glucose and lactose were added, were compared.

It was shown that there was a distinct peak followed by a depression in the pH and titratable acidity, in meat peptone mash media containing an excess of glucose, levulose, galactose, lactose, or saccharose, undergoing fermentation by *B. welchii*, which precludes the possibility of regarding the change in direction of such curves as proof of freedom from sugars. It was seen that 5% glucose was an excess for the culture in this test; that more than 2% gave evidence of inhibition; that 1% was completely exhausted. The escape of volatile acids was shown not to be the cause of the recessions in acidity, but that some of the acid first formed was probably destroyed. Such recessions in acidity, in the presence of an excess of fermentable sugar, were too small to confuse qualitative tests in fermentation. The limiting pH values for glucose, levulose, galactose, saccharose, and lactose were approximately the same, as were the titratable acidity for all but lactose, showing that *B. welchii* does not produce as much acid from lactose as from other sugars.

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**The Diphtheria Bacillus and Morphologically Similar Bacilli. Differential Characters and Diagnosis.**

*J. E. Dauvergne, Rev. d'hyg., Paris, 44:826, Sept., 1922.*

The true diphtheric bacillus produces acidity with glucose, levulose, galactose and maltose, but not with sucrose. It grows throughout the entire height of a Veillon tube and its cultures are actively hemolytic. It may be long, medium or short and virulent or avirulent for

guinea-pigs or birds. It grows well on coagulated serum and is Gram positive. It occurs in rows, clusters, etc. Short bacilli are by no means rare. In the Veillon tube, the diphtheria bacillus forms fine colonies not predominating in the aërobic zone, but distributed throughout the tube. The pseudodiphtheric bacillus develops only in a zone 2-3 mm. wide near the surface. This test is excellent for differentiation, but requires too much time (4-6 days). Moreover, it does not distinguish *Bacillus diphtheriae* from *B. cutis communis*. The author's medium consists of sterile horse serum, 100 c.c.; 30% sterile, aqueous solution glucose, 10 c.c.; sterile concentrated tincture turnsol, 30 gtt.; sterile 10:1000 sulphuric acid, 3 c.c. The medium is placed in Petri dishes. *B. diphtheriae* may be practically differentiated from the pseudodiphtheric bacillus by acidity, produced with glucose by the former and with sucrose by the latter.

For determining hemolysis, the unknown bacillus is inoculated in a medium consisting of 1000 gm. water, 10 gm. meat extract, 20 gm. peptone and 5 gm. NaCl. One or 2 drops of liquid containing human red cells, or those of the rabbit, guinea-pig, horse, sheep or monkey, are added and the mixture is incubated at 37° C. Diphtheria bacilli soon hemolyze, the pseudodiphtheria bacillus produces no hemolysis, even in 7 or 8 days, and *B. cutis communis*, if hemolyzing at all, does so only in 5 days or more. The diphtheria bacillus hemolyzes in less than 6 hours to less than 3 days, and, in all cases, in less than 4 days. *B. diphtheriae* must be differentiated from the pseudodiphtheric bacillus, *B. xerosis* and *B. cutis communis*.

In obtaining material from the throat, the lips, cheeks or tongue should not be touched and saliva should be avoided. *B. cutis* may be neglected in examining angina or for germ carriers. In the latter case, a single Petri dish may serve for 2 patients, the dish being marked off into 2 halves with chalk. In all other cases, a dish containing glucose medium, and one containing sucrose medium, must both be inoculated. *B. cutis* produces red colonies in both dishes, *B. diphtheriae* in the glucose medium only, after 24-36 hours' incubation at 37°, the dishes being placed cover-side down. The colonies produced by the pseudodiphtheric bacillus in glucose are grayish, irregular, grouped in globules or lozenges, soft and elevated in the center. *B. cutis* forms red colonies more slowly, their borders may be dentate or crenelated, and gray or yellow pigment may occur. Both the diphtheric colony and that of *B. cutis* are umbilicated and of regular outline. *B. xerosis* grows slowly and forms acid with glucose, levulose, galactose and sucrose.

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**The Immunity Reactions with a New Artificial Race of *Bacillus Coli*.**

*Paul Fabry, Ann. de l'Inst. Pasteur, Paris, 36:654, Sept., 1922.*

Ordinary *Bacillus coli communior* may be modified by growing in tubes containing increasing quantities of phenol up to a limit of 0.2%. The bacilli are transferred every day, cultivation being thus continued for a month. Bacilli so cultivated lose the power of producing indol in Dunham's water-peptone medium. The newly acquired character may be transmitted for at least 16 months. The modified

bacilli produce antibodies strictly specific for the new race. The agglutinins so obtained do not react in any way with ordinary *B. coli*. The modified bacilli are agglutinable by a normal anti-*coli* communior serum, the racial characteristics being thus preserved. The modification is best shown by the loss of the indol-producing ability, the digestive function (production of diastases or other catalyzers) having been altered. The modification is not of a degenerative character. Bacilli not adaptable to the phenol medium are eliminated, the modified character being transmitted by those which survive. Bacterial races are thus plastic and subject to the general laws of evolution.

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**Salt Effects in Bacterial Growth. II. The Growth of *Bacterium Coli* in Relation to H-Ion Concentration.**

*James M. Sherman and George E. Holm, J. Bacteriol., 7:465, Sept., 1922.*

In their previous work on the effect of neutral salts in different concentrations on growth of *Bacterium coli*, the authors showed that the optimum salt concentration was 0.20 m. in 1% peptone. The experiments were carried on at pH 7.0.

In following up this work, the authors attempted to find out what effect various H-ion concentrations would have on the neutral salt action. In their present experiments, as well as in their former ones, the rate of growth was determined by the time that expired between inoculation and the first sign of turbidity. The medium used was 1% peptone, to which various amounts of salt had been added, and the H-ion concentration adjusted by means of concentrated HCl and NaOH solutions. They found that at an optimum salt concentration (0.20 m.) there is very little difference in the rate of growth over a wide range of H-ion concentration varying from 5.3 to 8.3 on the pH scale.

While *B. coli* would rarely grow at a pH 4.8 in 1% peptone at 37° C., it grew quite readily when NaCl was added to the same medium to make a 0.20 m. solution. Although the widening effect of the pH limit is not general for all bacteria, it is still more pronounced on *Bacterium alkaligenes* than upon *B. coli*. On the other hand, a salt which lowers the rate of growth (e.g. sodium citrate) narrows the limits of H-ion concentration at which *B. coli* will grow.

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**My Method of Search for the Diphtheria Bacillus in the Bacteriologic Verification of Diphtheria.**

*M. Pergola, Ann d'igiene, Rome, 32:629, Aug., 1922.*

With swabs from supposedly diphtheritic patients or carriers, the cultures were first made by smears upon Löffler's serum and the emulsion prepared in tubes containing 1-2 c.c. sterile broth. Then with 5 large loopfuls of this emulsion (equivalent to 2-3 drops) the author made isolation cultures in solidified egg serum, and afterward enrichment cultures by adding to the same tube in which the emulsion was first

made 4-5 c.c. of one of the fluid substrates, which are designated I and II. The constitution of the solidified egg serum was normal blood serum (ox, horse, sheep), 50 c.c., solution of sodium chlorid (0.8%), 50 c.c., solution of potassium tellurite (2%), 1 c.c., yolk of egg, 1. The mixture became solid in the coagulator when exposed to a temperature not exceeding 85°-90° C. for approximately 1 hour. The enrichment substrates were thus constituted: Substrate I was like the medium above described but did not coagulate; Substrate II consisted of blood serum 100 c.c., solution of potassium tellurite (2%), 1 c.c., yolk of egg, 1. These mediums did not permit the loss of a single microbe when any were present. The cultures prepared as above were then placed in a thermostat at 37° C. and examined after 15-20 hours of development.

The examination consisted of bacterioscopic investigations made by means of preparations selected from the colonies eventually developing and stained by the old Neisser method, somewhat modified: (1) cold staining for 10-15 seconds of the preparation, already fixed by flame in Neisser's acetic methylene-blue; (2) washing with distilled water; (3) treatment for 10 seconds with Lugol's solution, with or without the addition of 1% of lactic acid; (4) cold staining for 10-15 seconds with a solution of vesuvin at 2:1000 or of chrysoidin at 1:300. The polar granules appear stained dark blue, almost black, and the bacterial body an ochraceous yellow.

The treatment with Lugol's solution has the twofold aim of eliminating the metalloid tellurium granules deposited in the bacterial body (which obstruct the demonstration of the polar granules) and of fixing upon these in some sort of manner the stain, which remains more permanently stable, so that the successive staining of the foundation with vesuvin or chrysoidin fails to replace it.

The author's investigations, uniformly controlled by cultures in Löffler's serum in order to arrive at a comparative judgment, have demonstrated the overwhelming superiority of his own method, which permitted him to trace the diphtheria bacillus in 45.80% of the total of 300 specimens examined, while Löffler's serum gave this result in only 16.76%.

Furthermore, with these mediums alone, there were positive results in 29.04% of cases, as against not one positive result with the Löffler serum alone.

Even excluding the cases recognized as positive in consequence of the enrichment culture, which in the total of specimens examined reached 13.47%, the superiority of the solidified egg serum medium over Löffler's serum remains notable, since the latter gave only 16.76% of positive results while the former gave 32.33%.

The same conclusion is reached in considering the total of positive cases, for, exclusive of those placed in evidence by the enrichment culture, which reached the approximate proportion of 30%, the solidified egg serum medium revealed 70.58%, Löffler's serum 36.60%.

The enrichment culture, which allowed of recovering about 30% of positive cases which would otherwise have remained unrecognized, showed itself to be of especial value in the case of carriers, in whom the diphtheria bacilli are lodged in very limited numbers: indeed, one single specific microörganism present in the enrichment fluid will suffice for the culture to give a positive result after the necessary amount

of time, so marked is the predilection of the substrate for the diphtheritic bacillus, to which it permits a far more active and vigorous multiplication than to the concomitant organisms. Of these latter, moreover, the culture rids itself with time, while offering, on the contrary, such favorable conditions of preservation to the Klebs-Löffler bacillus that this is still found in abundance after several months.

The search for diphtheria bacilli effected with these new cultural methods reveals their prolonged persistence in individuals who have suffered from diphtheria, as well as the existence, in a notable proportion, of carriers generally, demonstrating the urgent necessity of earnest study and effort to find a means of freeing in the most effective manner possible the bearer of the specific organism from its presence; otherwise a really efficacious prophylaxis will never be attained.

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**Some Antigenic Relations of the Bipolaris Septicus Group of Bacteria.**

*Lee M. Roderick, J. Infect. Dis., 31:313, Oct., 1922.*

Diseases of various animals, such as the horse, ox, sheep, hog, fowl and rabbit, have been described, and their etiology given as the bacteria of the bipolaris septicus group. Their pathogenicity is, however, not yet clear. The symptoms and the lesions of the diseases are similar, and the bacteria isolated agree in morphology and cultural characteristics. The present study was made to compare immunologically, the various strains of the organism by means of the complement-fixation reaction and use of serum of hyperimmunized animals. Cultures of these organisms are nonproteolytic; they do not form gas from carbohydrate, though acid is produced from most; lactose is not fermented by them and litmus milk is unchanged. Cultures are non-motile, Gram negative and aërobic.

The experiments consisted in the preparation of a number of specific immune serums from rabbits, using a single culture strain on each animal and testing for specificity of the serums against cultures from various hosts by means of the complement-fixation test. Rabbits were immunized by vaccines and live organisms.

Besides the rabbits a horse, which was also used, developed complement-fixing substances for the respective antigens, but the rate of development was slow. Serums prepared from sheep, fowl, rabbit and cavia origin gave reactions indicating no difference in antigenic character. Those of porcine and bovine origin were also grouped together. The presence of specific complement-fixing substances makes it appear that there are 2 strains or types of bipolaris septicus bacteria, a bovine-swine type and an ovine-avian-rabbit-cavia strain.

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**A Simple Method of Isolating the Enterococcus from Fecal Material.**

*A. Finocchietti, Rev. Sud.-Am. de endocrin. etc., Buenos Aires, 5:361, Sept., 1922.*

The diplococcus or pneumococcus (Fränkel) frequently found in the intestine in pneumonia, and sometimes in pulmonary lesions, is

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identical with the enterococcus described by Thiercelin, which has been called *Streptococcus enteritidis* by Escherich. It is constantly found in the intestine, even in normal individuals; the number of organisms is increased during disease. It generally assumes the form of a lanceolated diplococcus in normal feces, and appears as a short streptococcus, capable of forming long chains, in pathologic conditions and in cultures. Bacillary forms may also be found, particularly in old cultures.

The isolation of this organism from feces presents difficulties, due in part to the invasion of other species, which rapidly cover the surface of the culture medium, and conceal the colonies. Finocchietti and Dessy have evolved a method of avoiding this disadvantage. The procedure is based upon the greater resistance to certain temperatures possessed by the enterococcus, in comparison with that of the other microbes found in fecal material. The results are constant and the technic simple. A fragment of fecal material approximately as large as a grain of rice is placed in a broth-peptone tube, and incubated at 37° C. for 12-24 hours. It is then placed in a paraffin drying apparatus for 6-8 hours, or even longer. The culture is then resown on agar, which is incubated at 37° C.; other cultures are made 1 hour and 2 hours later. At least 1 of the 3 sowings will contain the enterococcus in pure culture.

Similar results may be obtained by heating the broth culture in a water bath for 5 minutes; a temperature of 65°-66° C. should not be exceeded. However, the results by this method are less constant, and a pure culture is not always obtained. If a culture is sown on agar before it is 5 or 6 hours old, and presents a homogeneous growth, or if isolated colonies of fecal bacteria are placed in paraffin for 6-8 hours, and incubated at 37° C. for 24 hours, examination by transillumination will reveal numerous small colonies of pure enterococcus. Enterococcus has always been found by this method, and is apparently a constant element in the intestinal flora.

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**Melitococcosis in Argentine Goats.**

*Raul Dessy and Enrique Lorenzelli, Rev. Sud.-Am. de endocrin. etc., Buenos Aires, 5: 320, Aug., 1922.*

The findings in a case of Malta fever inspired the examination of the goats in the vicinity, whose milk was considered to have been a factor in the spread of the contagion. According to the report of the English Mediterranean Commission, 50% of the goats of Malta, 43.3% of those in the south of France, and 7-14% of those in Florence were carriers of melitococcosis.

All the goats used for the experiment were subjected to the intradermal reaction, and to serologic and bacteriologic examinations. The cutaneous test was carried out with a strain of *Micrococcus melitensis* which had been cultured in broth, filtered and sterilized. The reaction in the case of experimentally infected animals was scarcely perceptible, and consisted in a small zone of edema and slight reddening of the skin. A positive reaction was obtained in 15% of the animals tested. Blood was drawn from these animals and from 4 normal controls, and

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cultured in broth and agar. Agglutination tests were carried out with agar cultures 24 hours old, emulsified in physiologic solution. The results were completely negative. The tests were repeated with goats which had not undergone the cutireaction, with negative results. A small coccobacillus was obtained from the blood of a goat whose cutireaction had been positive, and which had died 6 days after the test. Cultural and serologic examination of the organism proved that it was not *Micrococcus melitensis*.

The goats examined were thus proven not to be carriers of melitococcosis. Further experiments are required to determine the possible rôle of such animals in the spread of the disease. The Burnet intradermal reaction which was employed did not give the expected results, owing either to lack of specificity of the test or to the fact that the melitensis cultures used failed to have the antigenic properties necessary for the preparation of active filtrates.

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**The Relation of Vitamins to the Growth of a Streptococcus.**

*S. Henry Ayers and Courtland S. Mudge, J. Bacteriol., 7:449, Sept., 1922.*

The authors experimented with the water-soluble vitamin B and the fat-soluble vitamin A in their relation to the growth of a pathogenic streptococcus. In their first experiment, they used 3 media: (1) 95% alcoholic yeast extract plus peptone, which should contain water-soluble B; (2) extract from yeast residue plus peptone, which should not contain water-soluble B; (3) extract of regular yeast plus peptone, which should contain water-soluble B of the yeast. The growth of the streptococcus on the second and third medium was good, while on the first it was scant. The same experiment repeated with Osborn and Wakeman method for extracting the water-soluble B from the yeast yielded the same results. A third experiment was made with yeast, from which the water-soluble B was removed by Lloyd's reagent (fullers' earth), only a little of the vitamin apparently remaining in the filtrate. The streptococcus grew well on this medium.

These results lead the authors to conclude that water-soluble B is not the growth promoting substance of yeast, at least for the streptococcus used in their work. The growth promoting substance in cabbage extract, used by the authors successfully for the growth of streptococcus, is attributed to the large amount of reducing sugar contained in cabbage (1.4%). The same growth was obtained in parallel tests with glucose solutions, incorporated in the peptone medium.

Fats and oils, even in very small amounts, promote the growth of streptococcus. Mineral oils, which are not supposed to contain fat-soluble A, promote the growth of streptococcus, as well as vegetable oils which contain the fat-soluble A vitamin. The authors therefore conclude that either the growth promoting property is not due to fat-soluble A, or that this vitamin is also present in mineral oils, or that the stimulation is due to different causes in the vegetable and mineral oils.

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**The Streptococcus of Strangles.**

*Brocq-Rousseau, Forgeot and A. Urbain, Ann. de l'Inst. Pasteur, Paris, 36:646, Sept., 1922.*

The authors have endeavored to determine whether various races of streptococci may be differentiated by complement fixation. Serum very rich in antibodies was prepared by means of an antigen consisting of streptococci killed with alcohol-ether, 1 cg. culture being mixed with 20 c.c. normal saline solution. The bacteria were first partly mixed, with the aid of glass beads, in a tube of flask, the mixture being finally made up to the required volume. About 5 gm. fresh bacteria are needed to yield 1 gm. bacteria killed with alcohol-ether. The suspension obtained is thus 5 times as rich in bacterial bodies as the antigen usually employed. The titrations and deviation reactions were made according to the technic of Calmette and Massol. The complement-fixation reaction proves to be a satisfactory method for differentiating the streptococci of strangles from all other streptococci. The streptococcus of strangles secretes a hemolysin active for equine red cells, and frequently for the red cells of the sheep and guinea-pig. Other streptococci do not produce this hemolysin. Streptococci of human origin sometimes produce a hemolysin identical with that secreted by the strangles streptococci. The latter may be clearly differentiated by means of the complement-fixation and hemolysin reactions.

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**Use of the Pétroff Medium for Detecting Tubercle Bacilli in Effusions and Urine.**

*E. Moreau, Rev. de la tuberc., Paris, 3:385, Aug., 1922.*

To detect tubercle bacilli in urine, the sediment obtained by simple centrifugation is homogenized with an equal volume of 4% soda solution and the mixture again centrifugated, acidified, and the sediment inoculated into the medium. For very purulent urine, more soda may be added and left in contact with the sputum for as long as 4 hours, if so required. Positive results may be obtained in a month after inoculation. They are thus less rapid than with sputum, which requires 20-25 days, but quicker than inoculation tests in guinea-pigs.

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**New Method for the Isolation and Cultivation of Tubercle Bacilli Directly from Sputum.**

*Jean S. Valtis, Presse méd. hellénique, Athens, 3:316, Sept. 1, 1922.*

The isolation and culture of tubercle bacilli is at the present time possible only after experimental inoculation of guinea-pigs, and it requires at least 6 weeks to isolate tubercle bacilli. However, by the aid of the new culture medium of Petroff, tubercle bacilli may be iso-

lated directly from the sputum and obtained in pure culture in 8-14 days. Considerable clinical importance attaches to this new procedure, since it renders possible the demonstration of the bacilli even when present methods are ineffectual.

Petroff's medium is prepared as follows: Fresh meat (veal), devoid of fat or tendon, is ground fine in a sterile mortar, and 250 gm. of this mass is mixed in a sterile vessel with 212 c.c. sterile distilled water and 37.5 gm. sterile glycerin, the mixture being constantly stirred with a glass rod; the whole is then allowed to stand overnight in the ice-box. The next morning the mixture is filtered through sterile gauze. Then 16-20 eggs, previously immersed for 15 minutes in 70% alcohol in order to cleanse the shells, are broken into a sterile glass jar, the whites and yolks are mixed with a glass rod, and filtered through sterile gauze.

Of the meat filtrate 200 gm. is mixed with 400 gm. of the egg filtrate, well stirred, and for each 100 gm. of this mixture there is added 1 c.c. of a solution of gentian violet containing 1 c.c. of stain in 100 c.c. of 95% alcohol. After thorough admixture the medium is placed in test tubes, the mouths of which are stoppered with cotton, and allowed to coagulate after sterilization for 3 days in a Roux sterilizer. The mixture by this time becomes violet in color. The test-tubes are then stoppered with rubber.

The sputum is collected in sterile containers, is mixed with 3 times its volume of 4% NaOH solution, is well shaken, and is kept in the incubator for an hour at 37° C. The mass is then centrifuged for 15 minutes, and the whole of the fluid portion thrown away except the last 4 or 5 drops at the bottom of the tube, including the precipitate. The alkaline reaction of the latter is changed by the addition of 4-5 drops HCl. One drop of this precipitate is placed on a slide and stained by Ziehl's method. The remainder is inoculated on the surface of 4 or 5 test-tubes containing the new medium which are then immediately placed in the incubator at 38° C. In 8, or at most 14 days, colonies of tubercle bacilli appear in the form of small, dry, yellow points, which gradually form a dustlike film over the surface of the culture medium.

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### **The Significance of Elastic Fibers in Sputum.**

*Fernand Bezançon and Brodier, Rev. de la tuberc., Paris, 3: 398, Aug., 1922.*

The sputum is stained with Ziehl's stain, Weigert fuchselin and methylene-blue. The elastic fibers stain violet, bacilli red and the background blue. The elastic tissue occurs as fine fibers; larger fibers and large masses. The elastic fibers are detected better without homogenizing the sputum. Except in nontuberculous necrotic lesions of the lung, elastic fibers in the sputum are always accompanied by tubercle bacilli. The large masses or plates of elastic tissue are more numerous in proportion to the duration of the tuberculosis. Bacilli unaccompanied by elastic tissue are present in cured or nearly cured cases. The fibers disappear before the bacilli. The larger plates indicate a favorable prognosis.

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**Two New Species of Molds Found in the Human Body.**

*Giuseppe Berti, Policlinico (Surg. Sect.), Rome, 29:484, Sept. 15, 1922.*

From a granuloma removed surgically from the left leg of an 18 year old girl the author has isolated 2 hyphomycetes, one belonging to the genus *Penicillium* and the other to the genus *Acremoniella*, both representing new species. The first has been named *Penicillium burcii* and the other *Acremoniella bertii*.

The microbiologic characteristics of *Penicillium burcii* are the following: On Sabouraud's acid-glucose-peptone agar, even after only 2-3 days at a temperature of 18° C., there develop colonies having the appearance of unraveled cotton, white-yellowish in color, multiplying on the surface of the medium and soon coalescing; similar colonies develop on the surface of cultures made in Sabouraud's broth medium. If this broth medium is shaken after the first few days of incubation the cultures fall to the bottom of the medium in the form of flakes; but if the broth is shaken after the colonies have multiplied until they have formed a cuticle over the surface of the medium this cuticle sinks entire to the bottom of the test tube. On plain agar or broth mediums the parasite grows very poorly—slowly and sparingly.

Examination of a preparation made from material obtained from a culture tube shows very numerous small spores, weakly stained brown, not always disposed in chains (because, in stretching the surface of the culture by the introduction of the platinum loop, the conidia are detached from the conidiophores). Examination of a culture under a hanging drop shows numerous thick, short chains with very short, thin branches. The mycelium is branched, and in older cultures it is thick, very greatly subdivided by septa, and knotty. Depending upon the stage of development of the mycelium, there is observed at first the formation of short conidiophores on which there develop small spores, mostly round in shape and arranged in chains; at a later period in the development of the conidiophores there sprout out from the latter numerous branches, all bearing spores disposed in chain fashion. Occasionally the apex of a growing hypha shows a round, hyaline swelling, which soon becomes transformed into a branchlike outgrowth on which appear short chains of spores.

The *Acremoniella bertii* shows the following microbiologic characteristics: This mold also develops rather rapidly and quite well on Sabouraud's acid culture medium at 18° C. The colonies are greatly similar to those of the previously described mold (*P. burcii*), and exhibit the same properties when grown in Sabouraud's acid broth. This mold thrives poorly and grows very slowly in ordinary broth or agar. Microscopical examination of a hanging drop shows, in the earlier stages of development, that the mycelium produces conidiophores much thinner than those of the *Penicillium burcii*, not branching, very frequently provided at the apex with a single spherical conidium, smooth, at first hyaline but later assuming a dark brown color. The conidium is eventually thrown off and starts a new cycle in the reproduction of the species.

One must be careful not to confuse the younger forms of the *acremoniella* with those of the *penicillium*, for the 2 species are very



frequently found together. The sporulating hyphae of the penicillium have at their apex a round swelling which remains hyaline as long as it exists and then branches out; whereas the similarly situated swelling of the conidiophores of the acremoniella becomes transformed into a colored spore, spherical in shape, which eventually is thrown off to participate in the reproduction of the species. Microscopical examination of either Acremoniella or Penicillium is best effected in a hanging drop, without staining. For staining specimens obtained directly from culture tubes the best methods are gentian violet, Unna's blue, Giemsa's or Gram-Ribbert's. The spores and the hyphae are nonresistant to Gram. The 2 micromycetes, after inoculation in guinea-pigs either singly or together, reproduce quite faithfully the type of granuloma they cause in man.

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**The Fermentation of Pentoses by Molds.**

*W. H. Peterson, E. B. Fred and E. G. Schmidt, J. Biol. Chem., 54: 19, Sept., 1922.*

In the authors' experiments 25 cultures were studied representing *Aspergillus*, *Penicillium*, and *Mucor*. The destruction of sugar was used as a guide in the selection of pentose-fermenting molds. Of the 25 species of molds studied 16 were found to ferment the pentoses with rapidity. Most of the remaining 9 cultures grew slowly although 3 or 4 produced only a few mycelian threads. The best fermenters were found in species of *Aspergillus* and *Penicillium*, although a number of molds of these types attacked the pentoses but slowly. Species of *Mucor*, *Rhizopus nigricans*, and *Cunninghamella*, were also found to be very slow fermenters. Four or 5 days sufficed for the complete destruction of 4% solutions of the sugars with the most active forms of *Aspergillus* and *Penicillium*. No marked difference manifested itself in the rates of fermentation of the 2 pentoses. Carbon dioxide and mycelium represented the major portion of the sugars consumed. The percentage of total carbon represented by carbon dioxide varied with the species and age of the mold. *Penicillium glaucum* produced about 70% as much mycelium as *Aspergillus niger* and about 25% more carbon dioxide.

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**Actinomycosis in a Fossil Rhinoceros.**

*Roy L. Moodie, J. Parasitol., 9: 28, Sept., 1922.*

The jaw of a fossil rhinoceros, *Aphelops*, from the Snake Creek Beds, Pliocene, of the northwestern part of Nebraska, shows a diseased condition. Moodie states that the pathologic area has all the appearances of an actinomycotic osteitis, and bears a remarkable similarity to modern examples of "lumpy-jaw." The preserved portion of the lesion involves the alveolus of the left large incisor tooth and is, apparently, the oldest and so far the only fossil neoplasm of a definite actinomycotic nature. In the specimen, the exterior is relatively firm, while the interior of the tumor is mealy in appearance with numerous necrotic sinuses. The sinuses channel out to the surface of the jaw and one had formed in the alveolus. Apparently near the center of the mass

nearly all traces of osseous structure were lost, due to the destructive activity of the ray fungus. There is no indication of healing, and doubtless the infection was active at the time of the animal's death, suggesting that the infection was of long duration.

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**Actinomycosis in Madagascar Rats.**

*M. Fontoyront and P. Salvat, Bull, soc. de path. exot., Paris, 15: 596, July 12, 1922.*

A brown rat presented abscesses of the tail and flank, ulceration of the testicles and lesions of the eye. At autopsy, numerous abscesses were found in all the viscera. The causative organism proved to be a new species of actinomyces, the first reported causing lesions in the rat. Cultures grow on glycerin-peptone-gelose, coagulated serum, glycerin-potato, glycerin-carrot and glycerin-turnip. Incubated at 37° to 38°, they appear in 30 days or thereafter. The growth was more abundant in rubber-covered tubes, and failed at ordinary temperature. Gelose-peptone with glycerin, glucose or maltose was the most favorable medium. On these media, the diameter of the first colonies did not exceed 2 mm. The cultures grow better after transfers. The filaments of the mycelium are very fine, dividing dichotomously; sometimes they are large, and may be long or fragmented. Various forms exist in the same culture. The filaments terminate in clubs, wavy fibrils, wreaths of fragmented cocci-like masses, etc. Some of the latter constitute chlamydospores. Other chlamydospores are intermediate. In order to secure cultures, well staining mycelium, wavy fibrils (flame-like fibrils), club-shaped hyphae or hyphae bearing conidia, must be planted. Gentian violet and eosin are suitable for staining. Transmission of the fungus to rabbits, rats and guinea-pigs was examined. Feeding of the pus produced numerous abscesses and death, which also occurred on intraperitoneal injection of pus or 28-day cultures. Intraperitoneal injection of large quantities of pus produced rapid death by acute intoxication. Rats are more susceptible than rabbits or guinea-pigs.

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**The Formation of Citric Acid and Oxalic Acid in Citromyces Cultures on Sugar. The Procedure for the Quantitative Estimation of These Acids.**

*W. Butkewitsch, Biochem. Ztschr., Berlin, 131: 327, Aug. 11, 1922.*

Citromyces has the property of forming citric acid and oxalic acid from peptone and from the salts of various organic acids. This raised the question of the reciprocal relationship between citric acid and oxalic acid in the cultures of these fungi on sugar. Both acids must first be estimated quantitatively. For this purpose the unequal solubility of their calcium salts in acids may be used. The separation of the citric acid and oxalic acid calcium may be accomplished by extracting the mixture of both salts with weak hydrochloric acid under circumstances which allow only the dissolution of the calcium nitrate, and

by means of a previous dissolution of both salts in hydrochloric acid followed by separation of the oxalic acid as a calcium salt under circumstances which allow no precipitation of calcium nitrate. If the acids are present as soluble alkaline salts, they are first changed into calcium salts and then separated. In old cultures on 10% solution of cane sugar with calcium carbonate and with a relative deficiency of nitrogen, the fungi, which have the power of forming citric acid, also accumulate oxalic acid in more or less significant amounts. The relative amounts of citric acid and oxalic acid in the cultures are in inverse proportion in most cases; with a decrease in the amount of the former there is an increase in the latter, and vice versa.

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**The Consumption and Formation of Citric Acid in Cultures of *Citromyces Glaber* on Sugar.**

*W. Butkewitsch, Biochem. Ztschr., Berlin, 131:338, Aug. 11, 1922.*

Citric acid is well utilized by fungi, especially *Citromyces*, as a source of carbon. The addition of calcium carbonate to the cultures of the fungus produces an abundant deposit of calcium citrate. If citric acid, either free or as the sodium salt, is added to the nutrient solution which contains sugar, it is used up by the fungus together with the sugar, in proportion to the extent of its development. On exhaustion of the citric acid fixed to the base, oxalic acid appears. The citric acid is the usual product of metabolism in the normal development of the fungus. The economic coefficient for the citric acid in weak solutions approaches that of the sugar. With increase in the content of citric acid in the solution, the economic coefficient of utilization is diminished. In solutions of high concentration, the fungus utilizes the citric acid in a forced manner and unproductively. When the fungus exhausts both the sugar and citric acid simultaneously, the economic coefficient rises to a markedly greater value than that of cultures on sugar and on citric acid alone.

With a combination of sugar and citric acid, an increase in the productivity of the metabolism may be demonstrated. The presence of citric acid in the cultures of *Citromyces glaber*, with ammonium nitrate as a source of nitrogen, eliminates the disadvantageous effect of nitric acid, which is distinctly visible in the cultures on sugar alone. The utilization of nitric acid by the fungus is promoted by the presence of citric acid.

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**Technic for Staining the Ameba with Iron Hemotoxylin.**

*Charles A. Kofoid, Sidney S. Kornhauser and Olive Swezy, China M. J., Shanghai, 36:406, Sept., 1922.*

Take a small amount of feces, mucus being the best; mix with a drop of normal saline on slide or cover-glass; while still wet put in hot Schaudine solution (60° C.) specimen side down; leave it in the

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solution 10 minutes or longer; place in 70% alcohol, and stain at leisure. Transfer to basin of clean water for 10 minutes. Place in 4% aqueous solution of ammonium sulphate of iron, for 1-3 hours. Wash in water freely. Place in Heidenhain hematoxylin (0.5% aqueous solution of hemotoxylin which should have ripened for at least 6 weeks, the longer the better, even though mold grow on it). Leave in the stain over night. Wash in water. Destain in 1.5% aqueous solution of ammonium sulphate of iron. Leave specimen in this solution 1-5 minutes. Wash quickly in water, place on glass slide, being sure to keep it wet, and examine it under the microscope. Sardinia cysts appear in about 8 minutes; ameba cysts in about 5 minutes; Cheloniastix cysts in about 3 minutes, and live ameba in about 1½ minutes. Run through alcohols, 30%, 3 minutes; 50%, 4 minutes; 70%, 4 minutes; 80%, 4 minutes; 90%, 4 minutes; 100%, 5 minutes. Clear in xyol for 1 minute or more and mount in balsam before it dries.

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**The Diagnosis of Intestinal Flagellates by Culture Methods.**

*Robert W. Hegner and Elery R. Becker, J. Parasitol., 9:15, Sept., 1922.*

Various workers, including Hegner and Becker, have grown the trophozoites of 4 species of human intestinal flagellates in a simple culture medium; these are *Chilomastix mesnili*, *Trichomonas hominis*, *Embadomonas intestinalis*, and *Enteromonas hominis*. The authors have used with great success the ovomucoid medium prepared according to the directions of Hogue. This medium consists of a mixture of white of egg and 0.7% normal saline solution. The various smear methods have been generally used in the diagnosis of intestinal flagellates, but the authors have demonstrated that the culture method is more efficient than the smear method. In a comparative study of the diagnostic value of these methods the authors obtained fecal specimens from 110 individuals. Trophozoites were found by the smear method in only 2 of these; whereas 8 of the culture tubes were positive. Stools from a carrier of *Chilomastix* were examined on 10 days at various intervals between Dec. 5, 1921, and May 4, 1922. Smears from these were positive for trophozoites on 4 occasions, but the cultures contained trophozoites on 8 days. Trophozoites of both *Chilomastix* and *Trichomonas* may be obtained from stools by the culture method after they can no longer be found by the smear method, although a very painstaking search might have yielded results.

Tables of results are given which indicate that the trophozoites of *Trichomonas* appear to be more viable than those of *Chilomastix*. Positive smears of *Trichomonas* were obtained 37½ hours after a stool was passed and of *Chilomastix* only 12½ hours after defecation. *Trichomonas* was obtained in culture from a stool 79 hours old, whereas *Chilomastix* could be cultivated only from 18 to 19 hours after the stool was passed. It is suggested that the great viability of the trophozoite of *Trichomonas* may enable this species to gain access to new hosts without the aid of cysts. Cysts of *Chilomastix* did not give rise to trophozoites in the culture mediums used.

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**Chilomastix Mesnili. Parasitologic and Clinical Study.**

*Raul F. Vaccaresza, Semana méd., Buenos Aires, 29:517, Sept. 14, 1922.*

Chilomastix is parasitic not only to man but also to other mammals, birds, reptiles, batrachians and fishes. *Chilomastix mesnili* (Wenyon, 1910) belongs to the class Mastigophora, subclass Euflagellata, order Protomonadina, suborder Monozoa, family Tetramitidae, genus Chilomastix. It is a piriform flagellate, sometimes rounded, and moves actively. The anterior extremity is broad and round, the posterior extremely threadlike. The dimensions vary, averaging about 10-15 microns in length and 4-7 microns in width. Ectoplasm and endoplasm are distinguishable. The nucleus is in the anterior portion of the parasite, with or without a central karyosome. Anterior to the nucleus 1 or 2 granules of chromatin are found, and the basal corpuscles, whence emerge the flagella and the chromophile lip of the cytostome, which extends along about half of the body of the organism. Like other protozoan parasites of the human intestine, this organism assumes cystic forms in the presence of conditions unfavorable to its development. Reproduction is by amitosis or direct binary division. Involutional forms may appear in unfavorable mediums.

The best stain is Heindenhain's ferric hematoxylin (Dobell's modification). The life of a culture varies between 2 and 10 days. The best medium is 1 part human serum and 3 parts Locke's fluid. Studies of the inoculability of the organism gave variable results. The vitality and power of resistance of the organism resemble those of *Trichomonas hominis*.

This organism is universally distributed, regardless of climatic conditions. In every case of proctocolitis the presence of *Chilomastix mesnili* should be suspected, until the nature of the parasite is established. As regards propagation and contagion, this organism corresponds to the other intestinal protozoa. Direct contagion is rare; usually infestation takes place by way of water, vegetables, or fruit. It is probable that flies also play a large rôle in the transmission of the parasites. Any alimentary or functional disturbance which injures the integrity of the intestinal mucosa acts as a predisposing cause.

The presence of these flagellates in sufficient numbers produces diarrhea and rectocolitis. Blood is usually found in the stools. There is a marked tendency to chronicity. Macroscopic examination of the feces is not a reliable diagnostic criterion, owing to the frequency of mixed infections. Microscopical examination will reveal the type of parasite. The best treatment consists in iodine enemas, and spirits of turpentine, administered by mouth and by rectum. The enema should be retained as long as possible; to relieve the pain, a small laudanum enema should be given previous to the iodine. Three illustrative case histories are cited.

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**Councilmania Lafleuri Not a New Ameba.**

*Herbert Gunn, J. Parasitol., 9:24, Sept., 1922.*

The description by Kofoed and Swezy of a supposedly new ameba occurring in the intestinal tract of man and hitherto classified



as *Entamoeba coli* has necessitated a critical study of this class of cases. Kofoid and Swezy claim this ameba is pathogenic and that it differs from *Entamoeba* in a number of characteristics which they have used as diagnostic in both the free and encysted stages. Gunn has had 8 cases, pronounced by Kofoid's laboratory as *Councilmania lafleuri*, which were studied carefully in the free and encysted stages, comparing them for checking purposes with specimens from *Entamoeba coli* infections, classified by Kofoid's laboratory as *Entamoeba coli*. In none of the diagnostic characteristics given by Kofoid and Swezy could Gunn find any difference between the so-called *C. lafleuri* and *E. coli*. His conclusions are: (1) that there is no foundation for considering *Councilmania lafleuri* a new ameba; (2) that the authors were dealing entirely with *Entamoeba coli*, being led into error by an incorrect interpretation of staining reaction, by according too much weight to characteristics of amebae in the motile state, and by production of artefacts in the preparation of specimens. Gunn agrees with Wenyon (1922) when he adds *C. lafleuri* to the long list of synonyms of *E. coli*.

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**Notes on *Embadomonas Sinensis*, Faust and Wassell, 1921.**

*Ernest Carroll Faust, J. Parasitol., 9:33, Sept., 1922.*

*Embadomonas sinensis* was recovered from diarrheal stools of Chinese patients in the Church General Hospital, Wuchang, and was described by Faust and Wassell under that name (1921). In general, the specific characters of *E. sinensis* agree with those of *Embadomonas intestinalis*, although differences are apparent. In the first place, there is not the marked differentiation between anterior and posterior flagella, which probably accounts for the smoother movement of the Chinese species. These flagella are definitely specialized in direction and probably in function, although as far as Faust has observed their movements are synchronized. They stain readily with Donaldson's eosiniodid preparation. There is a blepharoplast, lying an appreciable distance from the nucleus, at the base of each of the flagella. The nucleus is somewhat smaller than that of *E. intestinalis*. The organism divides by longitudinal fission, with separation of the daughter elements at the posterior end, even while the anterior organella are still in the process of division. After separation the daughter cells are at first pyriform, but soon become actively motile and assume an elongated shape.

*E. sinensis* has been found only in native Chinese at Wuchang while *E. intestinalis* has been found in Alexandria, Egypt and the United States. Both flagellates are associated with *Entamoeba dysenteriae* in diarrheal stools. The species seems to fit into the environment and same organic cycle as *E. dysenteriae*. Even in questionable cases where *E. dysenteriae* has not been demonstrated in the stool, the presence of *E. sinensis* may be indicative of amebic infection.

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**Cultivation of *Rickettsia Prowazeki*.**

*R. Otto, Klin. Wchnschr., Berlin, 1:1746, Aug. 26, 1922.*

Kuczynski's assertion that he has succeeded in cultivating *Rickettsia prowazeki* under anaërobic conditions has not yet been con-

firmed by others. The author demands of an authentic culture that it be specifically agglutinated by the serum of a typhus patient and by Rickettsia immune serum, that in lice experiments it cause the typical infection of the intestinal epithelium of the lice, that it immunize guinea-pigs against infection with typhus virus and in rabbit experiments that it produce agglutinins against Proteus X. So long as the behavior of the Kuczynski microbes in reference to these postulates is not known, Kuczynski's assertion that he has succeeded in the cultures is premature.

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**A New Modification of Spirochete Staining.**

*Renc, Prakticky lek., Prague, 2: 167, Aug. 1, 1922.*

The author uses 2 solutions for silver staining: (1) tannin 5, acetic acid 2, distilled water 40, and alcohol (96%), 60 gm.; (2) silver nitrate 5 gm., and distilled water. After staining with the first solution ammonia is dropped on until the brown spots disappear; then the slide is heated until the alcohol is ignited. With a Drigalski rod the fluid is spread in order that the alcohol may burn uniformly. An aqueous solution remains on the slide; this is washed off with distilled water to which a few drops of ammonia have been added (10 to 50 to a liter). Then the second solution is poured over and the slide is heated for a little while (often the brown color develops alone), irrigated with distilled water and dried. As a modification of the enrichment method for tubercle bacillus, equal parts are homogenized with lye and sedimented or centrifuged; 96% alcohol is added and centrifuged again. A little water is added to the sediment and stained by the foregoing method.

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**Tricercomonas Intestinalis and Enteromonas Caviae N.SP. and Their Growth in Culture.**

*Kenneth M. Lynch, J. Parasitol., 9: 29, Sept., 1922.*

Dobell considers the Tricercomonas intestinalis of Wenyon and O'Connor and the Enteromonas hominis da Fonseca to be one and the same flagellate. However, Lynch isolated a human flagellate, from the stools of a woman, which is apparently identical with the T. intestinalis Wenyon and O'Connor and this is sufficient evidence to allow T. intestinalis to be retained for the present as the intestinal flagellate described by Wenyon and O'Connor. From a guinea-pig, Lynch isolated another organism which was similar to the above in size, motion, shape, nucleus, cultural qualities, and general appearance of the organism, but closely resembled da Fonseca's Enteromonas hominis. This flagellate Lynch calls Enteromonas caviae n. sp. The specimen appears to have only 2 anteriorly directed flagella and the recurrent one does not appear to be adherent to the body. It often lies back over the body, but frequently is distinctly unattached and sometimes occurs in a group with the other 2. Gunn's findings indicate that there is such an organism as da Fonseca describes and lend support to the opinion that Enteromonas and Tricercomonas are distinct. Gunn found that the

human flagellate grew well in ascitic fluid diluted with 4 parts of 0.9% NaCl solution at 37° C. for 4 days, but transplants were not successful.

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**Cultivation of Trichomonas and the Question of Differentiation of the Flagellates.**

*Kenneth M. Lynch, J.A.M.A., 79:1130, Sept. 30, 1922.*

Barring a limited number of special workers, the conception of the whole of the medical profession is probably confused no more by any question than that of the intestinal protozoa. Careful study of unstained material will serve to differentiate Trichomonas from any other organism. When fresh and active, the flagella movements and undulating membrane are characteristic. After exposure and cooling, it loses the action of these parts and assumes a peculiar ameboid undulating form in which protoplasmic waves of broad and blunt or long and finger-like proportions progress, with diminishing size from anterior to posterior end. When determining the number of flagella, for the possible dividing of the genus, the most careful staining is necessary. The usual process depended on for this differentiation is the iron-hematoxylon method.

Trichomonas is a widely and highly prevalent inhabitant of the body of man and is being extensively treated as a pathogenic organism. There exists only circumstantial evidence of any harmful effects from it or even of its true parasitism. The ease with which it can be grown artificially, its feeding habits, its high prevalence in the healthy and its long continuance without resulting disturbance in the human body indicate that it is a harmless commensal. For a proper judgment of its clinical significance, the organism must be differentiated from others now confused with it. In culture in the same material, trichomonads from the human mouth, vagina and intestine have not been certainly differentiated in this study. There exists no proof that trichomonads of other animals are identical with those of man, and at least some of them are certainly distinct.

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**Bilharziasis in Morocco. Distribution of *Bullinus Contortus* and *Planorbis Metidjensis*. Comparative Epidemiologic Study of the Tunisian (Gafsa) and Moroccan (Marrakech) Foci.**

*E. Brumpt, Bull. soc. de path. exot., Paris, 15:632, July 12, 1922.*

Vesical bilharziasis, although common among Senegalese troops stationed in Morocco, is rare among native Moroccans. However, a case was proved at Marrakech in 1922, the patient being a child of 10. The author found *Bullinus contortus*, a host of *Bilharzia*, at Marrakech. *Bullinus* prefers shade and pure, running water. It may be found under stones, leaves, etc., and sometimes in very shallow water. It adheres closely to its chosen support and probably feeds upon microscopic vegetable matter. Adults are 9-11 mm. long. Ova are laid on stones or leaves in a single layer containing 8-14 ova. The population of Marrakech is 100,000. *Bullinus* is very abundant there, but bil-

harziasis is rare. At Gafsa, Tunisia, whose population is but 5000, *Bullinus* is infrequent, but bilharziasis common. The fact is not due to climate, to composition of the water nor to the presence of the other host (*Planorbis*). *Bullinus* may really be more abundant at Gafsa than supposed. The difference in the incidence of bilharziasis at Marrakech and Gafsa appears due to differences in local custom, the Gafsa population being agricultural and living in close contact with local water sources, while that of Marrakech is composed largely of merchants and workmen living much less in contact with water. *Planorbis metidjensis*, reported as the Portuguese host of *Bilharzia*, was found at Tangier and several other Moroccan points. *Bullinus* was not found at Tangier, Casablanca, or Fez.

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**On the Duration of Life of *Clonorchis Sinensis* Infecting the Animal Body.**

*Masatomo Muto, Japan Med. World, Tokyo, 2:224, Aug. 15, 1922.*

Since 1918, the author has artificially infected various animals with *Clonorchis sinensis* and attempted to determine the duration of its life. Many of the animals died before the necessary time elapsed; however, the results obtained with dogs which lived a sufficient time are reported. Those animals which did not harbor the parasites were fed with the second intermediate hosts of the parasites having the encysted larvae, and feces were examined until the eggs of the parasites were found. Then feces were examined once or twice a month for the presence of the egg. There were only 3 dogs which survived over 2 years and observations on these dogs form the basis for the author's report.

The first dog lived 2 years, 8 months and 21 days; the second, 3 years, 3 months and 26 days; the third, 4 years, 1 month and 19 days from the first infection and 3 years, 6 months and 15 days from the second infection. The results show that there are no signs representing senile changes in *C. sinensis* parasitized in dogs for 2 years. In Case 1 the worms were all thin and small, some of them so atrophied that they appeared not to be able to live long, while the others still appeared nearly normal. In Case 2 some of the parasites were still nearly normal but the majority were markedly atrophied. In Case 3 the atrophy was so marked that even the viscera were hardly recognizable. There were a few worms, the uterus of which still contained a few eggs.

Comparative study of the stained specimens shows that at first the body becomes thin and small, at about the same time the testes and ovaries become atrophied. In the advanced stage the testes and uterus and ovaries are so atrophied that they become almost invisible and finally the worm dies. There are some worms which die before undergoing physiologic senile changes, but the majority begin to undergo the senile changes after living in the host for 2½ years. Then they die from atrophy. When they die, they are passed into the intestine through the common bile-duct.

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**A Note on Heterophyes Nocens as a Distinct Species of Trematode Parasite.**

*Clayton Lane, Lancet, London, 203: 505, Sept. 2, 1922.*

The measurements given by Cort and Yokagawa differentiating *Heterophyes nocens* from *Heterophyes heterophyes* were those of the muscular organs, or of the body as a whole, which is chiefly a muscular structure. Since the degree of muscular contraction alters the size and shape materially, the author feels that the evidence is not strong enough to justify revision of the judgment that the name *H. nocens* must lapse as a synonym of *H. heterophyes*.

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**Three New Species of Holostomidae.**

*John E. Guberlet, J. Parasitol., 9: 6, Sept., 1922.*

Guberlet describes in detail several new species of Holostomidae: (1) *Strigea aquavis* n. sp. found in the loon (*Gavia immer*) and the ringbilled gull (*Larus delawarensis*). *S. aquavis* differs from the other species of this genus in size, shape of the body, the relative sizes of the suckers, and the distribution of the vitellaria. Specimens of this trematode range in length from 2.5 to 3.5 mm. A definite constriction marks the division between the cephalic and caudal regions. The cup-shaped cephalic region contains the oral sucker, acetabulum, and the leaflike adhesive organ. Within the caudal region are located the reproductive organs, the excretory system and the intestinal crura. The vitellaria form a dense layer in the ventral half of the caudal region of the body. Small vitelline canals arise and pass dorsad to form the vitelline reservoir between the 2 testes. The vitelline duct passes dorsad from the reservoir and empties into the oviduct in the region of Mehlis' gland.

(2) *Hemistomum gavium* nov. spec. found in *Gavia immer* differs from other species in the relative sizes of suckers and the distribution of the vitellaria. The oral sucker is 60 microns in length and 80 microns in diameter. The acetabulum is 70 microns in diameter. The adhesive disk is 135-175 microns in length and 0.1 mm. in breadth. The numerous vitellaria are distributed in small groups. In the caudal region they are ventral and extend from the posterior end forward around testes and ovary. In the cephalic region they are generally distributed around the adhesive disk and acetabulum and well up toward the anterior end. The vitelline duct arises ventral to the testes, passes upward and enlarges into the vitelline reservoir, which is located between the testes. A small duct extends from the reservoir and empties into the oviduct in the region of the oötype and Mehlis' gland.

(3) *Hemistomum confusum* n. sp. found in the ringbilled gull (*Larus delawarensis*) is very similar to the *H. gavium* in many structures. However, the vitellaria have a more definite structure in this species than in *H. gavium*. The outlines of the glands are more distinct, and are generally distributed throughout the caudal region, especially posterior to the testes and anterior to the ovary, the latter area being almost completely filled with the glands. In the cephalic



region the vitellaria are generally distributed posterior to the adhesive disk and gradually become fewer in number and disappear before they reach the ventral sucker. The vitelline material is collected into the reservoir which is located between the testes and a duct passes from the reservoir and empties into the oviduct in the region of the oötype.

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**Linguatulids Parasitic in Monitors. The New Genus Sambonia.**

*Fernand Noc and George S. Giglioli, J. Trop. Med. & Hyg., London, 25:276, Sept. 1, 1922.*

Tongue-worms have been reported only from African monitors, and have been classified by various workers. The species described by the authors possesses external morphologic and internal anatomic characteristics which are sufficient to establish definitely and satisfactorily the taxonomic position of the Linguatulid found in the lungs of *Varanus niloticus*. The tubular uterovagina, long and much convoluted, at once places it in the subfamily Porocephalinae; its cylindroid body and its small acuminate cephalothorax with hooks arranged in trapezoidal formation indicate that it belongs to the section Sebekini of Sambon's classification. The imbricative annuli, the hooks provided with chitinized guards, the position of the female genital opening on the fifth body ring, and the spined eggs show that it belongs neither to any of the 3 genera (*Sebekia*, *Alofia*, *Leiperia*) now constituting the section Sebekini, nor to any other known genera of Linguatulidae. It is therefore the representative of a new genus of the Sebekini, for which the authors propose the name *Sambonia*. The species under consideration was first discovered by Lohrmann and will henceforth be known as *Sambonia lohrmann*.

The great merit of the new classification is that it follows the natural system, and a proof of its soundness is that, though the various subfamilies, sections, genera and species have been based solely on morphologic and anatomic characters, they show a remarkable zoölogic distribution or host correlation hitherto unsuspected. Different structural types strictly correspond to different host groups. This host specialization is carried out even to the species.

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**Massive Natural Infestation of the Senegal Genet by Larvas of *Porocephalus*.**

*F. Noc, Bull. soc. de path. exot., Paris, 15:621, July 12, 1922.*

The genet, a kind of civet cat, is found in the Dakar region. A carcass submitted for examination presented massive infestation with larvas of *Porocephalus armillatus*, all the thoracic and abdominal viscera except the bladder being affected. The organisms infesting the genet differ from those described by Hoyle as infesting *Proteles cristatus*. Hoyle's organisms were contained in connective tissue cysts, the author's not. Again, Hoyle's parasites were convex ventrally, the

author's specimens being concave. Noc reviews the morphology and characteristics, mainly from the available literature, with illustrations on plates, and gives a complete host index.

## 1e. IMMUNOLOGY, SEROLOGY AND HEMATOLOGY

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### The "Activation" of Body Cells and of Bacteria.

Wolfgang Weichardt, *Klin. Wchnschr.*, Berlin, 1:1725, Aug. 26, 1922.

Protein therapy causes only a change in reaction of the organism and its aim is an increase of functional capacity; a stimulation of inhibitory nerves may cause a decrease of functional capacity. Especially interesting are the activations which change and for the most part decrease the threshold of irritation for known specific toxins, such as adrenalin, pilocarpin, strychnin, phenol, salicylic acid and mercury. The increase in functional capacity comes about by a direct action on the cells, through humoral processes, or by action on the peripheral or central nervous system. To determine the reasons for certain increases of functional capacity, the author chose parasites which with reference to their ferment exchange are very well adapted to the body. Streptococci do not increase abundantly on nutrient mediums which are made up of uncomplicated, chemically definite constituents, even when simple nitrogen-containing groups, such as carbohydrates and salts, are added in abundance to such nutritive mediums; but after the addition of slight amounts of abiuret extractive substances they show an abundant growth, active fermentation and an influence on toxin formation. The extractive substances are obtained by the digestion of the stomachs and intestines of animals. If lactic acid is added to the macerated organs before their digestion into an extract, substances are obtained which stimulate growth still more; also by the preliminary infection of the animals with Friedländer's bacilli, or from pure cultures of Friedländer's bacilli themselves. The activating abiuret substances are effective even in very great dilutions but have an optimum of action, and when the concentration is increased above this they inhibit growth.

The effect on ferment function depends on the concentration of the extract; its optimum varies for different strains and also for the different ferment functions. Increase of toxic action can be demonstrated only for certain concentrations; on higher concentrations there is a decrease. The same substances which cause an activation of the bacteria may also decrease their reproduction and metabolism, depending on their distribution. This decrease depends on their concentration and on the sensitiveness of the ferment function. Recent observations on activation in the intestinal canal followed by serious disturbances, confirm the author's observations on streptococci; he believes that with higher concentrations the ferment functions of the intestinal bacteria may also be paralyzed, and that, therefore, the same substances which activate the bacteria of infection may in higher concentrations also act as protective substances. Their presence in the body is, therefore, often important and their removal not desirable. If they are not completely removed, what remains may have an activating effect on certain bacteria.

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**The Biology of the Male Sexual Cells.**

*Isematsu Tsukahara, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34: 444, Aug. 25, 1922.*

Metschnikoff and Landsteiner established the possibility of producing a specific antitoxin against the spermatozoa and found that spermatoxin is efficacious not only against heterogeneous spermatozoa but also against spermatozoa of the same species and of the same animal. This establishes a unique biologic position of the sexual cells in the organism. The same observation was also made by Dunbar in plants and fishes. The sexual cells partly lack the specific characters and represent heterogeneous protein. It developed that intravenous injections of sexual cells in animals can cause severe toxic reactions and even death; male animals are much more sensitive to standard testicular substance than females; of the latter the pregnant animals show the greatest degree of sensitiveness. The question arises, to what extent the organism normally produces antibodies against this. These antibodies might exist as components of the blood. Thus the assumption was justified that in the bodies of females after conception specific testicular antibodies are produced. The author's researches sought to determine the reaction of the serum of stallions, geldings and mares to testicular substance. The intravenous injection of highly concentrated testicular extract into cats and guinea-pigs caused toxic symptoms, the extract from horses being much more powerful than that from steers. Cats were more sensitive than guinea-pigs, and pregnant females so much so that a nonlethal dose interrupted pregnancy and caused death of the fetus. The serums of 29 horses and 2 steers gave negative results with testicular extract of horse and steer in complement-fixation and precipitation tests; on the other hand, with the same serums the Abderhalden reaction (dialysis method) was always positive.

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**The Nature of Specific Toxins.**

*Peter Bergell, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 121: 231, Aug. 24, 1922.*

A specific toxin is that chemical substance which causes toxic symptoms in a group of individuals suffering from a certain disease, while other individuals are affected by it only a little or not at all. Up to this time to a certain extent the only specific toxin has been Koch's tuberculin extract. To be sure, the symptoms of immunization, the idiosyncrasy of vaccination in the broadest sense, especially autovaccination, and also anaphylaxis can be regarded from the standpoint of specific toxicity; but these cannot be caused experimentally and according to definite laws as can tuberculin reactions. It is assumed that tuberculin is a substance that intervenes catalytically in chemical processes that have been initiated by the tubercle bacillus and the tuberculous tissue. But a ferment that originates directly or indirectly from the bacillus may turn it into a virulent poison, just as a slightly toxic albumose may be broken down into a more toxic peptone; or tuberculin may enter into synthesis with another substance which comes directly or indirectly from the bacillus and transform it into a stronger toxin.

The question can be cleared up by way of synthetic chemistry only if: (1) substances are found which can be administered to animals; and (2) other substances are found which are toxic for animals previously treated in this way but for no others. These toxins are to be sought for in the group of tropa-alkaloids. Atropin is fatal to man in small doses, but both the components which are easily obtained from it hydrolytically, tropin and phenylhydracrylic acid, are almost harmless in comparison. The synthesis is easily brought about, and mydriatic and miotic action of tropa-alkaloids are obtained in analogy with tuberculin.

The question now is: Is tropic acid a specific toxin for the animal charged with tropin or, conversely, is tropin a specific toxin for the animal laden with tropic (phenylhydracrylic) acid? The organism can act on both with its chemical forces. It can oxidize and esterize the acid at the alcohol group, or decarboxilize, esterize or anhydriize at the opposite point. Tropin can be esterized, etherized, demethylized, probably even oxidized. Glycuronic acid pairing can play a part in both. It has been found that there is a component action of the type of the specific toxin. Tropin is really a specific toxin for the tropic-acid animal. Habituation must also be taken into consideration; high doses can be reached both of tropin and tropic acid. They are therefore parallel to tuberculin in the specificity of their toxic nature and habituation to rapidly increasing doses. A specific local action must also be considered. In order to adopt this method with different bodies, different things must be clearly understood: (1) the refinement and time limitation of the doses; (2) the determination of the efficacious dose; (3) the minimum lethal dose; and (4) the chemistry of the individual processes.

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**Observations on the Properties of Bacteriolysants (D'Herelle's Phenomenon, Bacteriophage, Bacteriolytic Agent, etc.). I.**

*Wilburt C. Davison, J. Bacteriol., 7:475, Sept., 1922.*

The bacteriolysants were obtained from the filtrates of stools of infants suffering from bacillary dysentery of Flexner type, acute intestinal infection, otitis media, and faulty feeding. The bacteriolytic activity of these filtrates was tested by adding various dilutions of each filtrate to cultures of *Bacillus dysenteriae* (Flexner) grown in 1% peptone water, incubated 2-12 hours at 37° C. The degree of lysis was confirmed by the occurrence of "moth eaten" or "sensitive" colonies in subcultures on agar. In several instances the determination of lysis was also verified by a plate count before and after the action of a bacteriolysant. The reduction of visible organisms was found to be proportional to the degree of lysis. The author is not sure whether the reduction is altogether the result of the bactericidal action of the bacteriolysant or partly due to the inhibition of growth.

These filtrates were bacteriolytic for one or more of 27 strains of *B. dysenteriae* (Flexner and Shiga type), and also for typhoid bacillus. The author considers D'Herelle's phenomenon nonspecific; a bacteriolysant from a patient's stool may not be as active against the organism causing that individual's disease, as against other strains. The fact

that an active bacteriolysant was found in the stool of a patient the day before his death, militates against the theory that it plays a part in immunity or defense-mechanism of the body.

The bacteriolytic activity of a bacteriolysant is decreased by passage through a culture of *B. dysenteriae* grown in peptone water for 18 hours, and killed at 60-65° C. for 1 hour; also by passage through sterile peptone. The filtrate is not affected by heating at 60-67° C. for 45-60 minutes. The optimum reaction for production of lysis is at a pH of 8.0-8.2. The bacteriolysants acted alike on saline or peptone suspensions of *B. dysenteriae* (Flexner) provided the reaction was the same. Young cultures were more susceptible to lysis than old ones. The addition of 1 c.c. N sodium hydroxid to 4 c.c. bacteriolysant destroyed its bacteriolytic activity. Bacteriolysants were not pathogenic for rabbits, and had no therapeutic effect when administered to 12 young children suffering from bacillary dysentery.

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**Observations on the Nature of Bacteriolysants (D'Herelle's Phenomenon, Bacteriophage, Bacteriolytic Agent, etc.). II.**

*Wilburt C. Davison, J. Bacteriol., 7:491, Sept., 1922.*

The author carried on for 42 generations, subcultures of "moth eaten" or "sensitive" colonies, obtained originally by the action of a bacteriolysant on a dysentery culture. The colonies not affected by the bacteriolysant are called in contrast, the "resistant" strains.

The media in which the sensitive strains of *Bacillus dysenteriae* were grown, the salines in which they were washed, and suspensions of disintegrated or ground up sensitive strains were all strongly bacteriolytic. The lytic principle would therefore appear to be both extracellular and intracellular. The sensitive strains are lysogenic for numerous generations. Though the filtrates of normal *B. dysenteriae* may be slightly bacteriolytic, the lysogenic property is not passed on in subcultures. The author is of the opinion that the lytic principle in D'Herelle's phenomenon is an enzyme. He rules out trypsin as there was no bacteriolytic activity of a solution of trypsin on *B. dysenteriae*. Trypsin liquefies gelatin which is not true of the bacteriolysants of the sensitive strains of *B. dysenteriae*. The amount of the bacteriolytic enzyme produced by a culture can be increased by age, by growth on special media, and by contact with intestinal secretion, tissue extracts, and leukocytes. This enzyme not only dissolves organisms but favors the multiplication of bacteria which produce the enzyme. In this way, the bacteriolytic principle is carried from generation to generation.

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**Elementary Bacteriophages of the Shiga Bacillus.**

*Oskar Bail, Wien. klin. Wchnschr., 35:722, Aug. 31, 1922.*

It has already been shown that the strains of bacteriophages are not uniform in their action on a special strain of Shiga-Kruse bacilli, but that they consist of several partial bacteriophages which can be continued in pure cultures and which are distinguished as "small,"



"medium" and "large" by the size of the holes which they make in agar plates of Shiga bacillus. It was not possible to make any further differentiation of the bacteriophage strains by the plate method (agar, gelatin), but it was possible to further separate the partial bacteriophages which produced the same size holes by bouillon culture. For example, on inoculation of the large strain "Krato" in bouillon, it often grew in spots while the bouillon remained clear and afterward a sediment was formed. In other cases the bouillon remained clear a long time even when many bacilli were added to it, and only became uniformly turbid after 8 to 10 hours. Bacilli cultivated from the turbid bouillon proved resistant to the bacteriophages which their development produced and kept this resistance on further cultivation. But the bacteria cultivated from the spotted cultures were not resistant. The specificity of this resistance can only be utilized for the separation of elementary bacteriophages. If plate cultures are made of the bacteria grown in bouillon with large bacteriophages and treated with mixed bacteriophages, in spite of the resistance to the large bacteriophages, not only do small holes develop, but also large ones, proving that there is a third elementary bacteriophage present which also causes large holes. Such a division of mixed bacteriophages into 3 elementary bacteriophages was possible not only with Krato but with 4 other strains, but not with all. The author distinguishes 2 forms of the large bacteriophages, a g-form (Shiga grows in spots in effective bouillon dilutions) and a  $\gamma$ -form (growth in bouillon delayed, later making the bouillon turbid). The bacilli from the  $\gamma$ -bouillon are  $\gamma$ -fast, but the g-bacilli are not  $\gamma$ -fast. In order to classify a bacteriophage it is necessary to determine its effectiveness against heterologous bacteria. G-bacteriophages and  $\gamma$ -bacteriophages proved ineffective against staphylococci, streptococci, anthrax, hog cholera, proteus and cholera. Their behavior toward Shiga, Flexner, Singer's stool bacteria, the cattle colon strain "Cord," typhoid and mouse typhoid bacilli was tested by the Fuerth method; agar plates liquid at 50° to which the bacteriophages and their dilutions were added. On every plate smears of 8 different species of bacteria were made. (To be continued)

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(1c—250)

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**Transmissible Autolysis of Bacillus Anthracis, without the Intervention of the Supposedly Bacteriophagic Virus.**

*Cesár E. Pico, Semana méd., Buenos Aires, 29: 448, Aug. 31, 1922.*

Pico has disproved the hypothesis of a bacteriophagic virus. He was able to produce transmissible microbial autolysis by means of ferments (papayotin heated to 90°-100° C. and leukocytic ferments) proven to be free from the hypothetic ultramicrobe. However, the fact that not all strains of a given microorganism are able to dissolve in series appears to furnish support to the theory of bacteriophagy. Pico therefore carried out the following experiment: A carbuncle culture, in suspension in physiologic solution and heated for an hour to 83°-95° C., was sown on agar inclined tubes. A normal loop of carbuncle bacilli was suspended in 10-12 c.c. distilled water slightly alkalized with a drop of a 1:5 solution of  $\text{CO}_3\text{Na}_2$ . Within 6 days the water had cleared by autolysis, leaving a slight deposit of bacillary residuum and spores; 2 c.c. of this liquid were added to a fresh suspension of carbuncle

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bacilli; clarification was complete in 48 hours. A subsequent suspension cleared in 24 hours. In order to remove all doubt, the passages of the bacilli were suspended in physiologic solution, the lytic principle being enriched by successive filtrations by Berkefeld filters; clarification was complete in 24 hours at 37° C.

Thus lysis in series was obtained. However, not all strains possess this property. Temperature and the influence of certain antiseptics affect the cultures.

Pico claims to have proven the possibility of producing transmissible autolysis of *Bacillus anthracis* without the agency of a bacteriophagic element. The lytic principle is contained and elaborated by the same organism. In other words, bacteriophagy consists in an activation of the normal autolysis of the bacteria. Nutritive vitiation, suggested by Bordet and Ciuca, is an effect rather than a cause of the dissolution of the bacteria.

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(1e—251)

(1e—251)

### **The Action of Antidiphtheritic Serum in Experimental Diphtheria of Rabbits.**

*Kazufusa Sato, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34: 365, Aug. 25, 1922.*

Recently it was observed that under certain conditions parenteral injections of nonspecific protein yield results similar to those obtained with specific antigen or serum. Pfeiffer first clearly defined these effects as an increase in resistance. In tracheally infected animals, especially rabbits, the therapeutic effect of diphtheria serum has not been studied extensively so far. The author sought to test the efficacy of the specific serum in comparison with normal serum. Inoculations were made with a virulent strain of diphtheria bacilli, so as to ensure the development of abundant toxin. Twenty-three rabbits were inoculated intratracheally and all succumbed. If, within an hour before the inoculation, 125 anti-toxin units (or possibly less) were injected, the animals were immunized, but double this amount was required for immunization if given simultaneously or within an hour after inoculation. Controls showed that it is possible to immunize rabbits with normal horse serum and to cure the disease within certain limits. This could be done with 1 c.c. horse serum and within 8 hours following inoculation. After an injection of diphtheria serum the animals reacted by improvement of general condition and diminution of local symptoms (dyspnea).

Dietrich assumed that it is possible to save the animals only up to 6 hours after infection. He maintains, therefore, that the efficacy of diphtheria serum is limited to the incubation period. Dietrich's injections were only subcutaneous; the author's divergent results are due to intravenous and intramuscular injections by which good results were obtained with large doses of antitoxin. It was possible to save animals 8 and 12 hours after infection. Hence, this is viewed not as an immunizing effect with diminishing efficacy during the incubation period, but as a true curative effect. The subcutaneous injection of diphtheria serum does not bring the curative principle into equal play. The anti-toxin effect must be specific since under the same experimental conditions normal horse serum failed absolutely. With a decrease in amount

of antitoxin the certainty and time limit of a possible cure are proportionately modified. If the antitoxin values found efficacious in experimental rabbit diphtheria are calculated on the basis of human weight, it must be concluded that therapeutic antitoxin doses have not yet been attained.

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(1e—252)

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**The Tissue Reaction and Formation of Antitoxin in Horses after Intrapulmonary Injections of Diphtheria Toxin.**

*Renjiro Kaneko, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34:424, Aug., 1922.*

In the preparation of an efficacious immune serum, care must be taken in the use of the antigen. Under otherwise similar conditions respecting the species and the individual, the dose and virulence of the antigen and the frequency of the injections, marked differences in the production of the specific antibodies result from the mode of infection. In preparing a potent diphtheria serum in horses the intramuscular or subcutaneous injection of the diphtheria serum has proved more effective than the intravenous route.

In the author's work the conditions of the formation of antibodies in intrapulmonary injection are studied by histologic examination of the lung tissue and by tests of distribution of antitoxin in the different organs (especially the lungs) and in the blood. Repeated toxin injections in horses cause chronic proliferating inflammation of the lungs accompanied by hemorrhages. According to Lurje and Homén these changes correspond to the reaction of the lung to a not highly virulent toxin. Marked degenerative changes, those characteristic of a highly concentrated serum, were not observed. Antitoxin content in the organs of highly immunized horses is always less than that of the blood serum and depends largely on the amount of blood in the organs. The antitoxin quantity after intrapulmonary injection is much greater in the venous blood than in the arterial. In the focal pulmonary lesions a much greater amount of antitoxin is found than in the other organs. In the spleen, on the other hand, the amount of antitoxin is very small and it cannot be shown that the spleen takes any special part in antitoxin production. The lungs cannot be considered as the chief place of formation of antitoxin; this function devolves on the whole organism. In fact the lungs withdraw antitoxin from the blood by storing it, perhaps changing it through oxidation.

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**Prophylactic Treatment for Rabies by Means of Standardized Glycerinated Virus.**

*James McIlvaine Phillips, J. Immunol., 7:409, Sept., 1922.*

The author's study indicates that heat, oxygen, light, moisture and various chemicals cause the loss of virulence in rabies vaccines as they are usually prepared, and that when these factors are not present the virus remains active for amazingly long periods of time. The technic described below has been in use by Phillips for 5 years, and after 46 passages the virus still retains its original virulence. For prophylactic

treatments the author does not use virus which has been in storage over 6 months.

Young rabbits from a known source are inoculated intracerebrally with 0.015-0.075 mg. fixed virus suspended in salt solution. When the animal is completely paralyzed and appears to be moribund it is killed by bleeding. This reduces the amount of blood in the brain, lessens the amount of foreign protein in each therapeutic dose and produces less local reaction. To reduce the protein still further, the brain alone is used because the cord contains fewer infection units in proportion to its weight. After its removal the brain is weighed and rubbed to a smooth paste in a mortar. Glycerin is then slowly added and thoroughly incorporated until the total volume of fixed virus and glycerin has reached such a point that each 0.1 c.c. of the suspension contains 15 mg. of the fresh fixed virus. Various sized amber glass ampules are then filled up well into their necks with the glycerinated virus. Each ampule is put into a separate test-tube which contains a small pledget of nonabsorbent cotton to protect the neck of the ampule from breakage. The tubes are placed in cold storage for a few hours. The mouth of the test-tube is then crowded full of pyrogallic acid by ramming the tube into this material. The test-tube is then inverted and 2-3 c.c. 40% caustic potash solution are added, followed by a pledget of absorbent cotton, and a good quality of rubber stopper is tightly inserted at once. The object of this procedure is to absorb the oxygen in the tube. These units are stored upright in test-tube baskets at  $-2$  to  $-4^{\circ}$  C. until required, when, to make the dilutions used in the treatment of cases, a storage tube is selected which contains sufficient virus for the required number of doses. The tube is broken so as to remove the ampule without contamination. The contents of the ampule are flushed out into the proper amount of 0.85% salt solution, to which 0.5% phenol has been added and the resulting mixture is strained through gauze. The individual treatments may be sent in ampules, syringes or vials to places near the laboratory. A survey of cases given by the author shows 1 death out of 1540 cases which received prophylactic treatment for rabies with this glycerinated virus.

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### **Experimental Reproduction of the Specific Histopathology of Influenza.**

*George Baehr and Leo Loewe, Arch. Int. Med., 30: 307, Sept. 15, 1922.*

The following primary lesions were produced in rabbits by the intratracheal inoculation of Berkefeld filtrates of nasopharyngeal washings from early cases of influenza or of cultures of the filtrable punctiform bodies cultivated from such washings: (1) Congestion, edema and small hemorrhages in the mucous membrane of the trachea and bronchi. (2) Presence of a profuse, slightly blood-tinged, frothy, serous liquid in the lumen of the bronchi. (3) Diffuse, patchy distribution of red, jelly-like lesions throughout the lungs. (4) Intense congestion of a large part of the intervening lung parenchyma and acute emphysematous overdistension of alveoli. (5) Widespread exudation of serum and extravasation of red blood-cells from the

vessels, filling interstitial tissues and groups of alveolar air spaces. (6) Aplastic character of this exudate. (7) Aneurysmal dilatation of short stretches of capillaries and arterioles and sometimes closure of the lumen of these vessels at these sites by blood-platelet thrombi. (8) Tendency to early secondary invasion with pyogenic organisms, which then induce a rapid purulent infiltration, thereby completely obliterating the primary and specific picture of the disease.

These characteristics have all been observed in human influenza by pathologists who have had the opportunity to study the lungs of patients with fulminating disease and who died within the first few days of their illness before secondary infection had occurred. The lesions as they occurred in these early cases have been regarded as constituting a specific pathologic picture. The experimental lesions correspond with considerable accuracy to those of human influenza, and they cannot be confused with the changes produced by any other pathogenic organism either in human beings or in animals.

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**A Report on Pneumococcus Inoculation in New York State Institutions.**

*G. W. McCoy, H. E. Hasseltine, Augustus Wadsworth and Mary B. Kirkbride, J.A.M.A., 79:1128, Sept. 30, 1922.*

This study was conducted jointly by the Hygienic Laboratory of the U. S. Public Health Service and the Division of Laboratories and Research of the New York State Department of Health. Pneumonia, as it develops in man, occurs under conditions in which the susceptibility of the host and the virulence of the invading parasite are fairly evenly balanced; in the majority of cases the reaction of the tissues brings about a spontaneous recovery which is complete. The mortality varies greatly, ranging from 10 to 40%. It is quite conceivable that preventive inoculation might give rise to sufficient immunity to protect some, if not all, persons for a short time and under special conditions of exposure, but the fact that inoculation does afford material protection should be clearly demonstrated before it is advocated generally, and it was for this purpose that the present study was undertaken.

In the examination of all the specimens the most reliable method, that of inoculating a mouse, was used. In addition, the cultural method of Avery and the precipitin test of Krumwiede were used in some specimens. The death rate from pneumonia in the inoculated appeared to be much below that in the control group, but the same is true of the total death rate. The results were far from satisfactory and do not permit any definite conclusions. Nevertheless, they show that a relatively large number of cases of pneumonia developed after inoculation; furthermore, they show the development, in the inoculated group, of pneumonias incited by the 3 fixed types of pneumococcus used in the vaccine.

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**Studies on the Sheep-Pox.**

*M. Tsurumi, T. Toyoda and T. Inouye, Japan Med. World, Tokyo, 2:221, Aug. 15, 1922.*

In a pasture near Dairen, in February, 1922, there occurred a strange disease among a group of sheep that had been brought from

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a province in China. Spread of the disease was exceedingly rapid and soon the entire flock of 600 was attacked. The death rate was 43%. The authors, since the outbreak of this epidemic, have been studying and comparing small-pox and cow-pox with sheep-pox and also making studies of prophylaxis. The symptoms and courses are exactly the same as those of small-pox and cow-pox. Although the studies are not yet completed, they report the results obtained thus far.

The noxious virus passes through the Chamberland filter. Cutaneous, subcutaneous and intravenous inoculations of the materials obtained from the papules, vesicles, pustules, crusts and plasma of the diseased sheep gave positive results in sheep. The same experiments with the filtrates gave only positive results with the materials taken from vesicles and epidermis. As to the resistance of the virus, it was still positive after the papule was kept 35 days in an ice-chest at a temperature of 5-6° C., or the serous secretion of the pus was sealed in a test-tube and kept 71 days in the ice-chest. It is killed in 5 minutes in 1.0% carbolic acid and 7 minutes in 0.1% bichlorid of mercury solutions.

The sheep which once had the disease acquired immunity. Immunity is acquired not only by general infection, but by local exanthems, such as the emergency inoculations. The small-pox virus cannot infect the sheep directly, but when the human virus passes through a monkey, it can infect the sheep. However, the sheep were infected directly with cow-pox virus. Thus it is shown that there is not only very close relation between the viruses of human, cow and sheep poxes, but they appear to be identical. The infection experiment was not tried on human beings with sheep-pox virus which had passed through monkey, nor was sheep-pox virus tried directly on the cow. Therefore, it cannot be definitely said that they are one and the same virus.

After cow-pox had been inoculated into sheep, reinoculation with sheep virus gave negative results in a certain number. Immunologically, the viruses of human, cow and sheep poxes show specific characters, according to complement fixation tests, but results of precipitation reactions by boiling show that they have certain common characters. As to prophylactic measures, emergency inoculation is an effective method, but the sheep-pox virus cannot be kept for use when needed. Inoculation of cow-pox virus bestows a certain amount of immunity. The convalescent serum appears to be effective for the treatment of the disease.

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#### **On the Group Specificness of Antibodies in Anti-streptococcus Serum.**

*Ruth Tunnicliff, J. Infect. Dis., 31:373, Oct., 1922.*

Previous work had shown that sheep immunized with hemolytic streptococci from scarlet fever and erysipelas produced specific opsonins and agglutinins, while absorption tests also indicated that these organisms belong to distinct biologic groups. In opsonic, agglutination, and absorption tests on immunized sheep and rabbits it was demonstrated that immune sheep serum containing specific opsonins and agglutinins for hemolytic streptococci from scarlet fever, retained its specific antibodies in one instance for 11 months in the ice-box; in other cases

the serum was nonspecific when drawn, or quickly became so on standing in the ice-box, or was nonspecific in dilutions under 1:20. Some serum lost its agglutinating power rapidly on standing.

Rabbits immunized with frequent large doses of hemolytic streptococci from scarlet fever, tonsillitis and sinusitis, produced only nonspecific antibodies, while fewer and smaller doses of the organisms from scarlet fever usually produced specific agglutinins. Hence, these agglutination and absorption experiments with specific immune rabbit serum confirmed previous work done to show that most of the hemolytic streptococci associated with scarlet fever belong to a distinct biologic group.

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**The Mechanism of the Disappearance of Trypanocidal Substance in Patients with Liver Disease.**

*F. Rosenthal and R. Freund, Klin. Wchnschr., Berlin, 1:1748, Aug. 26, 1922.*

The following experimental findings indicate the truth of the theory that the disappearance of trypanocidal serum substances in cholemic forms of icterus is due to disturbances in the process of their formation in the places where trypanocidal serum bodies are produced. Neither bile nor the constituents of bile in maximum concentrations can influence the trypanocidal action of normal human serum. The latter also preserves its trypanocidal power after admixture with icteric serum, also in the cholemic medium of the severely icteric mouse. The reaction of the disappearance of trypanocidal substance in severe human liver diseases is dependent on the complement content of the serum; the trypanocidal serum substance does not have a complex character.

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**The Clinical Utility of Trypanocidal Serum.**

*J. L. A. Peutz, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:1544, Sept. 30, 1922.*

The author has examined the effects of the serum of normal persons and of patients with hepatic cirrhosis, grip, diabetes, cancer, ascites, and other diseases on mice infected with *Trypanosoma brucei*. The virulence of the trypanosome was first attenuated by passage through guinea-pigs, which were used as carriers for supplying the trypanosomes as needed. For infecting the mice, blood from the heart of a succumbing guinea-pig was diluted with sodium citrate solution; 0.1 c.c. of the citrate dilution was injected intraperitoneally into mice receiving 1 c.c. human serum just before or just after the blood injection. In no case was full survival obtained, notwithstanding large doses of human serum. Control animals were never injected with mixed blood, but were kept in distinct series. Apparently protective results could thus always be referred to the blood of a single mouse. In one series, human serum appeared to delay death to the tenth day, a mouse of the same series succumbing in 3 days when treated with serum from a case of hepatic cirrhosis. Results obtained with serum of diabetes, tuberculosis, and other diseases were not decisive. Tests were made with glucose and with heated serum.

The experiments show that human serum contains one or more substances which may destroy certain trypanosomes. The substance is thermolabile and acts by lysis. Glucose has no effect in trypanosomiasis of laboratory animals, either in vivo or in vitro. Ascitic fluid from hepatic cases is less trypanocidal than normal serum. The trypanocidal properties of normal serum may be diminished or destroyed by certain diseases, but not in a constant manner. The diminution is most marked in extensive hepatic affections. However, individual variations in the resistance of the test animals, and other factors which cannot be controlled, prevent very definite conclusions. The serum effects are thus far of purely theoretic interest and without clinical application. Eyre and Marshall's cure of sleeping sickness by injecting human serum intraspinally is explicable not only by the presence of antibodies produced by dead trypanosomes, but also by the action of the natural trypanocidal substance, which attacked *T. gambiense* not only in the blood, but especially in its refuge within the central nervous system.

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**The Leukocyte Formula and Susceptibility to Tuberculosis in Guinea-Pigs.**

*Berthelon and Delbecq, Rev. de la tuberc., Paris, 3:414, Aug., 1922.*

The mean leukocyte formula of the normal guinea-pig is lymphocytes, 33.6%; medium mononuclears, 17.6%; large mononuclears, 16.5%; polynuclears with 1 or 2 nuclei, 11.4%; with 3 nuclei, 10.3%; with 4 nuclei, 5%; with 5 or 6 nuclei, 3.9%; eosinophils, 5.5%; basophils, about 1%. Daily variations may occur. The total number of mononuclears may range from 54% to 81%; of large mononuclears from 11% to 28%; of eosinophils from 0.2% to 13%; and basophils from 0.1% to 3%. The large mononuclears may contain a vacuole at whose center is a strongly staining corpuscle. The inclusions are probably nuclear and red cell remains ingested by the cell. The large mononuclears do not appear to contain ferments capable of destroying tubercle bacilli and, therefore, probably serve to distribute them. No conclusions can be drawn concerning the occurrence of artificially produced increase in the mononuclears.

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**Alterations of the Leukocyte Formula in Tuberculous Guinea-Pigs.**

*Berthelon and Delbecq, Rev. de la tuberc., Paris, 3:416, Aug., 1922.*

The leukocyte formula of tuberculous guinea-pigs, representing the maximum reaction present on the seventeenth day after inoculation, consists of lymphocytes and medium-sized mononuclears, 27.1%; large mononuclears, 51.3%; polynuclears with 1 or 2 nuclei, 8.7%; id. with 3 nuclei, 6.4%; id. with 4 nuclei, 2.1%; id. with 5 nuclei, 1.2%; id. with 6 nuclei, 0.6%; eosinophils, 1.4%; basophils, 2.3%. The large mononuclears are increased throughout the course of the infection.

Nucleated red cells appear about the tenth day, increasing by the twelfth or thirteenth day to 12-15% of the total number of leukocytes. After the seventeenth day, not more than 1 red cell per 100 leukocytes can be found. The basophils are enormously increased in the terminal stage. In an animal dying on the forty-seventh day, the basophils were 6.5% on the thirty-first day; 18.2% on the fortieth, and 22.9% on the forty-fifth day. Experimental conditions may produce variations. For this reason, the normal formula should be determined before instituting experiments.

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**Vaccination of the Rabbit and Guinea-Pig against Tuberculous Infection.**

*A. Calmette, L. Nègre and A. Boquet, Ann. de l'Inst. Pasteur, Paris, 36:625, Sept., 1922.*

The authors worked with very virulent bacilli of bovine origin, rendered avirulent by growing for 14 years, with transfers, in a bile medium. These bacilli produced no infection when 100 mg. of the culture were injected into the rabbit heart, or 50 mg. into the guinea-pig heart. Intravenous inoculation of 20 mg., or preferably of 30 mg., of a culture of the bacilli protected the rabbit against infection fatal for the check animals in 50-75 days, provided the test animals were healthy. Bacilli injected into the blood collected chiefly in the spleen, liver and lungs during 10-20 days after the injection. They were not found in the kidney. From the twentieth day, they ceased to occur in the liver and bone-marrow, diminishing in other tissues until, after 2 months, they could no longer be found in any tissue. The tuberculin test remained positive for 4 months. The antibodies produced by injecting the bacilli increased for 3 months, then rapidly diminished. A similar resistance was developed in guinea-pigs. The artificial immunity gradually declines. In the rabbit, it entirely ceases by the sixth, in the guinea-pig by the fifth, month after the vaccination. It thus lasts but a short time although it may possibly be prolonged by periodic vaccination of the lymphatic tissues.

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**The Effect of Fractional Inoculations of Tuberculosis in Guinea-Pigs at Multiple Points.**

*Fernand Arloing and Lucien Thévenot, Rev. de la tuberc., Paris, 3:429, Aug., 1922.*

A total dose of 1 mg. bacilli, derived from human cases, was injected into the guinea-pig in various regions (neck, thigh, flank, pleura, etc.). The resulting infection is graver and more fatal than in inoculations made in a single site. Progress and date of death vary directly as the number of inoculation sites. The gravest infections result from inoculation into the serous membranes. The general effects of experimental inoculation are not modified by multiple inoculation, nor are appearances even remotely resembling Koch's phenomenon observed. These principles hold for all forms of multiple inoculation.

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**Gradual Diminution of the Virulence of Pulmonary Granulations of Inoculated Guinea-Pigs by Artificial Gastric Juice in Direct Proportion to the Duration of Treatment.**

*Ernest Fernbach and Georges Rullier, Rev. de la tuberc., Paris, 3:404, Aug., 1922.*

Granulations taken from the lungs of guinea-pigs inoculated with tubercle bacilli were placed in the authors' artificial gastric juice; 45-50 bacilli were present per field. Twenty granulations have about the same volume as 140 c.c. liquid, and 20 were used for each test. Tabulated results show that the virulence of the granulations diminishes in proportion to the duration of exposure to the test liquid. The virulence was entirely destroyed by exposures of  $\frac{1}{2}$ -3 hours at 52° C., and of 37-39½ hours at 15°.

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**Histologic Observations on the Destruction of the Tubercle Bacillus in the Subcutaneous Tissues.**

*Ada Ivetta Saggiori, Riforma med., Naples, 38:842, Sept. 4, 1922.*

Investigations were made with the idea of ascertaining whether tubercle bacilli are disintegrated by the animal organism. The author injected dead tubercle bacilli into certain guinea-pigs and living bacilli into others, from a culture in glycerinated broth, suspended in distilled water. Six days after the injection he took from 1 guinea-pig of each series the piece of skin and subcutaneous tissue corresponding to the nodule formed at the point of injection. The same procedure was carried out with other guinea-pigs after 2, 16, 21, 30 and 40 days from the time of injections. Six days after the injection a part of the dead bacilli injected (vaccine) were granular, while the live bacilli injected were still intact. Two days later some of the living bacilli injected were also granular. After 16 days there were very few intact bacilli, and even these were granular in the preparations made from the guinea-pigs injected with vaccine, the rest were bacillary fragments of an acid-fast character and Much's granules in great quantity; a few intact bacilli were found in preparations from guinea-pigs injected with living bacilli. After 40 days there were still some few Koch bacilli, of a streptococciform nature, in the preparations taken from the guinea-pigs injected with living bacilli; fewer acid-fast granules and Much's granules in the preparations made from the guinea-pigs injected with vaccine; after 60 days, there was here and there a bacillary granule, and this only in the sections of skin taken from the guinea-pigs inoculated with living bacilli. All the examinations were controlled by sections of sound skin of the same animals.

These experiments reveal that the subcutaneous cellular structure has the property of disintegrating, reducing to the Gram-resisting granular form, and dissolving, not only the dead Koch bacilli but also the living and virulent ones. The inoculation of vaccine composed of dead germs, therefore, provokes antigens in the circulation and is sufficient to immunize the organism.



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**Anaphylaxis and Immunity.**

*S. Metalnikov, Ann. de l'Inst. Pasteur, Paris, 36:632, Sept., 1922.*

Anaphylaxis and immunity are apparently contradictory. Since anaphylaxis is a general biologic phenomenon, it must be studied in invertebrates and plants, as well as in higher animals. The author has especially studied 2 caterpillars (*Galleria melonella* and *Cnethocampa pityocampa*), dilute horse serum being introduced into the celomic cavity. After this presumably sensitizing injection, a second was made in 12-14 days. No result was obtained, even with enormous quantities of horse serum. However, the caterpillars had been rendered extraordinarily sensitive to their own blood. Injections of the treated blood into the same individual, or into another sensitized individual of the same species, produced a sort of anaphylactic shock, the caterpillars manifesting excitement, active movements, convulsive contractions and death in 2 or 3 minutes, provided sufficient blood were injected. The longer the exposure of the blood to the air, the greater the toxicity, thus produced by oxidation. Small injections of the blood cause coma, with subsequent recovery. The sudden death is due to a coagulating effect of the oxidized blood. The tests with *Cnethocampa* were even more marked than those with *Galleria*.

Anaphylaxis may be readily produced in caterpillars rendered immune to the cholera vibrio. According to the quantity of the bacteria present in the second injection, immunity or death may result. The immunity produced is not effective against massive infection. Similar effects may be produced in guinea-pigs with injections of typhoid or tubercle bacilli, or with cholera vibrios. The body cells are rendered hypersensitive, if any heterologous albuminoid be injected. They then react more intensely when the antigen is introduced. During immunization, all the cells react against the bacteria or antigen introduced. If the hostile antigen reappears, the phagocytes actively attack it, all other cells also reacting. The result is an inflammatory, or suppurative, reaction. Under usual conditions, only a small quantity of the invading virus penetrates the skin or mucosa, the consequent reaction being sufficient to protect the organism. But the cells are oversensitized if the virus be introduced directly into the blood or body cavities. In this case, the reactions become violent, the result being the so-called anaphylactic shock. The phenomena are analogous to those accompanying burns—the more extensive the burn, the graver the consequent shock. There is thus no real contradiction between immunity and anaphylaxis.

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**Electrocardiographic Examinations of the Relations of the Vegetative Nervous System to Anaphylactic Shock.**

*Paul Hoefer and Arnt Kohlrausch, Klin. Wchnschr., Berlin, 1:1893, Sept. 16, 1922.*

To test the heart disturbances in anaphylactic shock and their relations to the vegetative nervous system, rabbits and guinea-pigs were sensitized and the electrocardiograms taken during and after the intravenous reinjections. In some of the animals the vagus was

excluded in the neck before the reinjection. In a third series of experiments the action of atropin on the shock was tested. In rabbits severe heart disturbances were the only symptoms of the shock, either slowing of the beat or disturbance of conduction, or both. There were no respiratory disturbances. The disturbance of conduction was manifested by negative T peaks, extrasystoles, variations in the regular ventricular systole, and lengthening of the P-R interval up to complete dissociation. Exclusion of the vagus had no effect, atropin had a transitory favorable action on the shock. In guinea-pigs, the heart symptoms only began after the beginning of respiratory disturbances but with exclusion of the vagus they began before the appearance of respiratory disturbances. The authors believe that in guinea-pigs the same toxic action causes the heart and respiratory disturbances. The cardiac inhibition and the disturbances of conduction show an involvement of the vegetative nervous system in the causation of anaphylactic shock, and this is also indicated by the better action of atropin.

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### **The Question of Allergy.**

*L. Karczag, Wien. klin. Wchnschr., 35:724, Aug. 31, 1922.*

Experiments on guinea-pigs artificially infected with tuberculosis showed that the same nonspecific factors lower and raise the allergy as in man; poor food, darkness, pregnancy, maize intoxication and large doses of benzol lower it; light, good food, thyroid substance, small doses of benzol increase it. The rule that prognosis is better with high allergy holds in animals as well as in man, but here too, as in man, there are exceptions. White guinea-pigs had higher allergy in the beginning than colored ones. But in the former the allergy gradually decreased, and in the latter it gradually increased, so that in 5 weeks it was the same in both; the swelling of the regional lymph glands was greater in the white ones. The mortality of the white ones was greater. There was the same difference between the white and colored guinea-pigs on simultaneous infection with tuberculosis and maize. The white guinea-pigs, therefore, could not utilize the higher allergy so well, and it was extinguished sooner. The pigment therefore seems to bring about a greater intensity of the allergy and greater duration, rather than to increase its absolute height. Hutinel as well as Moro and Hirsch have shown that tuberculosis patients, on intracutaneous injection of salt solution, develop a local reaction of a nature similar to the tuberculin reaction.

Former experiments of the author showed that this salt reaction is of 3 grades: hyperallergic, moderate and hypallergic, parallel in degree to the strength of the tuberculin allergy. Now the author finds that, selecting moderate allergic cases, the salt and tuberculin reactions are changed in the same way by nonspecific influences. Both reactions were increased by small doses of benzol, 3 gm. daily, or potassium iodid, 1.0 gm. daily for 18 days; decreased by injection of typhoid vaccine and large doses of benzol. Later experiments of Curschmann and Grover-Hecht also show, in general, a parallelism between the specific and nonspecific reactions.

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**The Technic of the Infection Method for the Production of Auto-Antianaphylaxis.**

*J. Piticariu, Spitalul, Bucharest, 42:192, July-Aug., 1922.*

Into a 1 c.c. syringe, 0.9 c.c. calcium chlorid solution is drawn, and then 0.1 c.c. blood is aspirated into the syringe from the ulnar vein of the patient. The syringe is shaken until there is a uniform intense red solution. The first injection is made with 0.001 c.c. blood, the second with 0.002 c.c., the third with 0.003 c.c., and so on, until end doses of 0.1, 0.2 and 0.5 c.c. are reached. Higher doses have no effect, cause painful infiltrations and weaken the patient. For the necessary dilutions the procedure is as follows: From the syringe which at first contained 0.9 c.c. of 1% calcium chlorid solution and 0.1 c.c. blood, 0.9 c.c. is emptied, so that only 0.01 c.c. blood remains in the 0.09 c.c. of calcium chlorid solution. Then 0.9 c.c. of the calcium chlorid solution is drawn into the syringe and well shaken. The color of this solution is clearer, and it now contains 0.01 c.c. blood in 0.99 c.c. of 1% calcium chlorid solution. An intramuscular injection of a tenth of this syringe introduces 0.001 c.c. blood. The doses are then increased by tenths. The first 5 injections are given daily, after that up to the tenth they are given every other day, and then in gradually increasing intervals of 2, 4, 5 and 6 days.

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**An Alimentary Leukocytosis in Its Relation to the "Crise Hémoclasique" of Widal.**

*W. Storm van Leeuwen, Z. Bien and H. Varekamp, J. Exper. Med., 36:415, Oct. 1, 1922.*

Counts of the number of white blood-cells at short intervals after the ingestion of a meal (meat, eggs, milk, rice, or butter) in normal individuals and in a number of asthmatics reveal the following facts: As a rule, a sharp fall in the leukocyte curve occurs within 1 or 2 minutes after the meal; generally the curve rises within 10-20 minutes, but often there is a second fall 30-50 minutes after the meal. This may be followed by a slow rise in the curve (physiologic leukocytosis). The first sharp fall is often accompanied by a similar decrease in red cells, the leukocyte formula is not changed, the blood pressure remains unchanged also, and this makes it probable that the leukopenia observed is only a manifestation of a change in distribution of the blood in different regions of the body. Not infrequently the leukocyte curve after the ingestion of food shows a form differing considerably from that described above. Counts of white cells made at intervals of 20 minutes in the same patient at different times but after ingestion of the same food show very different leukocyte curves. Such counts do not give evidence of the existence of a "crise hémoclasique" and consequently cannot be used to identify the causative agent of cases of hypersensitiveness to foodstuffs or drugs. Whether such an identification can be obtained if, instead of simply counting white cells, the whole complex of symptoms originally described by Widal as characteristic for a "crise hémoclasique" is used, remains undetermined by the work of the authors.

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**Trypsin Intoxication and Related Conditions.**

*H. Pfeiffer and F. Standenath, Klin. Wchnschr., Berlin, 1: 1933, Sept. 23, 1922.*

After severe burns and injuries from light, in anaphylactic shock and in hemolysin intoxication, ferments were demonstrated in the body which were probably the causes of this intoxication and which act upon the vessels. As trypsin absorbed in charcoal loses its toxic action, the author tried to protect the body from the action of trypsin by introducing the ferment and charcoal at different times and points into the circulation. In white mice, fluid Nankin ink, diluted 10-20 times, was absorbed from the abdominal cavity into the circulation, first exclusively by the reticulo-endothelial tissue of the liver, spleen and bone-marrow. From the circulation, fluid ink was precipitated in these organs in guinea-pigs and rabbits. After being given ink animals are protected from several times a fatal dose of trypsin if it is introduced through the abdominal cavity, not through the subcutaneous cellular tissue. This difference in the behavior of the liver, spleen and bone-marrow shows that the reticulo-endothelial apparatus of these organs is the point of attack of the ferment in intraperitoneal intoxication. But when fatal amounts of trypsin are given through the subcutaneous cellular tissue the protection fails completely. To explain this, the author used pyrrol blue instead of India ink, since it has a great affinity for the reticulo-endothelial structure of the connective tissue and lymph-glands, but only slight affinity for that of the liver, spleen and bone-marrow. White mice charged with pyrrol blue are, because of the lesser storage in the spleen and liver, less protected than those that have been given ink, but still they are considerably protected against toxin administered through the peritoneum; therefore the measure of storage of the protective substance in the liver and spleen is the decisive point. Pyrrol blue storage in the subcutaneous cellular tissue, in the muscles and lymph-glands does not protect against ferment given subcutaneously; here the reticulo-endothelium is not the point of attack of the trypsin. Ferrum oxidatum saccharatum given through the abdominal cavity is stored in the omentum, lymph-glands and spleen, and protects against ferment given intraperitoneally, but not against that given subcutaneously. The protection afforded by India ink, pyrrol blue and colloidal iron is directed against the ferment itself, but not against the products of its digestion. In hemolysin intoxication this preliminary treatment protects against fatal doses given through the abdomen, but not against retention uremia of the rabbit, photodynamic death nor skin burns. However, this does not argue against intimate interrelation of these forms of intoxication and of ferment intoxication.

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**Pharmacology of the Blood Serum.**

*Hans Handovsky, Klin. Wchnschr., Berlin, 1: 1752, Aug. 26, 1922.*

It was demonstrated in Trendelenburg's frog-vessel preparations that serum has a stronger vasoconstrictor action than plasma. This action is not due to adrenalin and has nothing to do directly with coagulation. But it is probable that the separation of the serum and corpuscles that takes place in coagulation, changes the colloid in such

a way that it acts on the different substrates. But blood-plasma takes on vasoconstrictor characteristics even without coagulation if the blood-platelets are destroyed. The action of freshly defibrinated blood, which, in analogy with anaphylactic shock, consists in causing central paralysis, fall of temperature, peripheral vasodilatation, and interference with heart action, is to be attributed to destruction of the blood-platelets. The late toxic action of the platelet-free serum, which develops 20 minutes after defibrinization, consists in causing a rise of temperature, peripheral change in the vessels, increase in systolic heart activity and increased tonus of smooth muscle fiber. This late toxic action has not yet been explained. Alcoholic extracts of serum have the same action as serum itself. It is probable that changes in the colloid condition of the blood or serum give to them certain actions.

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**Cow Serum as a Substitute for Colostrum in New-Born Calves.**

*Theobald Smith and Ralph B. Little, J. Exper. Med., 36:453, Oct. 1, 1922.*

The rapid absorption into the blood of agglutinins toward *Bacillus abortus* ingested in the colostrum, indicated that the immunity of the calves receiving colostrum is due to the protective antibodies which tend to accumulate in the colostrum up to the time of parturition. If this inference is true, the blood of the adult cow should also contain these various antibodies and might protect calves not fortified by colostrum. To test this hypothesis, 3 groups of calves were treated with the blood serum of the same cow in slightly different ways. In the first group of 5 calves receiving serum into the jugular vein and the subcutis, 3 died and a fourth was very sick. In the second group of 5 which received the same treatment plus serum fed in milk, none died. In the third group of 5 which received serum in the milk, 2 died.

The results indicate that the cow serum introduced both by way of the blood and the digestive tract replaced colostrum successfully. Simply feeding the serum, though only partially successful, appears superior to injecting it. When colostrum is withheld, the body becomes flooded with *Bacillus coli* types. After a calf has ingested colostrum or has been treated with serum, the invasion of the body is suppressed. The digestive tract, however, may not have been protected sufficiently to prevent scours or acute diarrhea from appearing after 1 or 2 days. In those animals that died, the serum, whether injected or fed, protected the internal organs against the invasion and multiplication of *B. coli* and other intestinal types and in this respect its protective action is equivalent to that of colostrum in those calves which die of spontaneous scours.

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**The Hemolytic and Coagulating Action of Metallic Ions.**

*E. Meneghetti, Biochem. Ztschr., Berlin, 131:38, July 29, 1922.*

Different metallic salts (Zn, Cd, Fe, Ca, Ni, Pb, Cu, Hg, Ag, Pd, Pt, Au) exercise an action on the erythrocytes due to the cations, which differs for the different metals and at different concentrations.

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Very low concentrations cause hemolysis, but higher ones cause coagulation. In both actions there are differences depending on the place which the metals occupy in the series of electric tension; the lower the tension of the solution the stronger the action. The influence of the cations is proved by the relations between hemolytic and coagulating activity, on the one hand, and ionic concentration, on the other. Any change in the latter brings about a parallel change in the activities, and of different compounds of a metal those which are the most strongly ionized are the most effective, both in hemolysis and coagulation. The physicochemic processes, the end-result of which is hemolysis or coagulation, develop with varying rapidity, depending on the temperature, concentration and specific activity of the metallic ions and on the special characteristics of the salt in proportion to the rapidity of the shifting of the phases of a very complicated balance. Probably certain special histologic pictures in blood-corpuscles fixed with some of the salts are to be ascribed to the varying rapidity of these shiftings. The physicochemic processes which tend to coagulation appear first and with many high concentrations develop so rapidly that the end-result is a sudden coagulation of the blood-corpuscles. If the concentration is not so high these processes do not develop so rapidly, and in the process of their development a certain degree of hemolysis takes place, and as the end-result there is coagulation of broken down fragments of blood-cells. At lower concentrations they develop still more slowly, and a greater degree of hemolysis takes place, which is shown by an increase in the viscosity of the hemolyzed fluid. At still lower concentrations even the increase in viscosity is no longer perceived. If with suitable chemical reagents enough of the coagulating agent is removed from the fixed blood-cells so as to reduce the concentration below the minimum for coagulation, then hemolysis occurs, which may also take place during the development of the processes that cause coagulation and also during the reversion of a coagulation that has already occurred. It may, therefore, be claimed that the metal in the fixed blood-corpuscle is still present as an ion and that probably the coagulation is caused by the formation of a compound or an ionic-protein adsorption product with the established characteristics of lability and reversibility and a different composition. As the result of the action of a positive electric charge, in general, physicochemic processes develop which tend to coagulation of the oppositely charged globular colloid. The rapidity and strength of these processes depend on the specific activity and the concentration of the metallic ions. With very rapid development coagulation occurs, with slow development the shifting of the charge of the globular colloids in a complex balance causes processes of flocculation that are manifested by hemolysis.

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**Prevention of Hemolysis Caused by Sodium Oleate by the Addition of Serum in Various Diseases, Particularly Malignant Tumors.**

*Herbert Kahn and Paul Potthoff, Ztschr. f. d. ges. exper. Med., Berlin, 29: 169, Aug. 19, 1922.*

The various endocrine organs are in some way connected with the processes of growth and development, and probably also with the formation of malignant tumors. The authors attempted to study this

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problem by experiments on the cytolytic properties of endocrine extracts. Of the various extracts investigated those yielding the maximum hemolytic effects were fresh aqueous extract of spleen, ether extract of thymus, and most of all, aqueous extract of pancreas. Heating to 56° C. for ½ hour destroyed the hemolytic property of all but the pancreatic extracts. On the addition of serum to the original extract there occurred arrest of hemolysis, this effect being most pronounced in aqueous spleen extract.

Comparative experiments with normal serum and serum of carcinomatous origin revealed the following: Half an hour following a hemolysis test with pancreatic extract the addition of 0.1 c.c. normal serum produced renewed, intense hemolysis; an hour later the addition of 0.08 c.c. normal serum produced complete arrest of hemolysis. The serums from persons with malignant tumors yielded the uniform result that with 1:8 dilution of pancreatic extract the addition of 0.25 c.c. carcinomatous serum caused arrest of hemolysis.

The only drawback was that it was not possible to utilize extracts of constant composition. Based on the demonstration of Korschun and Morgenroth that the hemolytic substance of the pancreas is soluble in alcohol and indestructible by heat, the authors extracted pancreatic juice with 5 times its volume of 95% alcohol and filtered the mixture after 2 hours. Repeated extraction with alcohol yielded a clear alcoholic solution which, even after prolonged standing, exhibited constant hemolytic properties. This solution (by which, after addition of normal serum, arrest of hemolysis could be illustrated most strikingly) was obtained, after boiling in acetone, as pure active substance in needle-shaped crystals grouped in tufts or clusters. These crystals melted readily at low temperatures, forming a light yellow, transparent solution; on standing this color deepened and looked much like sodium oleate. The melted crystals were hemolytic in the greatest dilutions and, both with normal and carcinomatous serums, exhibited the properties of fresh pancreatic extract. There was mild arrest of hemolysis in most febrile infectious diseases, in some hemolytic anemias, in malignant neoplasms and in cirrhosis of the liver. The lowest combining property, expressed in milligrams of oleic acid necessary to combine with 100 c.c. serum, was found in cases of malignant tumors (375 or less); combining values of 400 or 425 were rare, the only readings above this level occurring in 2 cases of healed cancer of the breast.

The differentiation of malignant tumors from hemolytic anemias, infectious diseases and cirrhosis of the liver is clinically and bacteriologically not difficult. Determination of the extent of arrested hemolysis by sodium oleate through the addition of serum from a suspected case now offers an additional valuable sign in differentiating malignant neoplasms.

The chemical or physicochemical processes involved in the reaction must now be determined. Oleic acid combines with certain constituents of the erythrocytes and of their cell wall, thereby changing the structure of the cell so as to allow the escape of hemoglobin; these constituents are mostly cholesterins. If the latter are added before the experiment no hemolysis occurs; the addition of calcium salts (which combine with the oleic acids) renders the latter ineffective. In most cases of malignant neoplasm (carcinoma) the calcium as well as cholesterol and lecithin content of the blood was considerably diminished. In the

arrest of hemolysis by sodium oleate through the addition of serum not only these 2 substances are concerned but there are undoubtedly various physicochemical changes at the same time. For instance, the surface tension of carcinomatous serum is lower than that of normal serum, and the meiotagmin reaction is due to physicochemical changes in carcinomatous serum. Perhaps the latter also contains hemolytic substances not present in normal serum. The less intense arrest of hemolysis by sodium oleate in infectious diseases may be explained by the presence of bacterial hemolysins. Staphylolysin is destroyed by heating to 56° C., but not streptolysin nor typholysin. Perhaps these bodies combine with some part of the substances concerned with arresting sodium oleate hemolysis. Similarly there may be active, in an organism affected with malignancy, 3 distinct but synchronous processes: (1) accumulation of substances which combine with unsaturated oleic acids within the malignant tumor and resulting diminution of these substances in the remainder of the body; (2) elimination into the organism of unsaturated (uncombined) oleic acids as products of metabolism of the malignant tumor, and (3) production of cytolytic substances within the organism as a defense against the malignant process.

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**Globulin and Albumin from the Same Blood Serum as Immunizing Antagonists.**

*R. Doerr and W. Berger, Biochem. Ztschr., Berlin, 131:13, July 29, 1922.*

In an exhaustive study of the structure of serum protein, one of the points to be decided was whether and how the individual parts mutually influence each other if they act at the same time on the same organism that has a capacity for reaction. It was possible to demonstrate almost absolute specific differences between euglobulin and albumin from horse serum. This fact constitutes the only preliminary condition for that peculiar phenomenon of interference which is noted when 2 or more antigens are administered parenterally simultaneously or in short sequence. Lewis abolished the sensitizing action of horse serum when it was mixed with larger amounts of the serum of other animals or man, even when relatively high doses of egg albumin were given. Dog serum behaves similarly with reference to egg albumin and the antigen which is present in the smaller amount is overcome by the other. This competition between the antigens represented a reciprocal relation determined only by quantitative relations between 2 antigens of different specificity, but evidently of equal intensity as an immunizing stimulant. Horse serum was divided into four fractions: (1) euglobulin A, between 0 and 33% saturation with ammonium sulphate; (2) pseudoglobulin B, between 33 and 50% saturation; (3) albumin C, between 50 and 66% saturation, and (4) albumin D, between 66 and 99% saturation. As there were the greatest differences between A and D both with reference to specificity and to intensity of antigen function, these were brought into competition. The control experiments on guinea-pigs showed on testing the anaphylactic condition after 21 days that equal and optimal doses of euglobulin and albumin did not seem to influence each other in antigen function. But

if the optimal dose of one antigen was given at the same time with a great excess of the other, the hundredfold excess of albumin D seemed to have practically no effect on the optimal sensitizing dose of euglobulin; on the other hand the antigen function of optimal quantities of albumin was completely abolished by the simultaneous administration of hundredfold quantities of euglobulin. Euglobulin can suppress albumin, but the converse is not true. There is no reciprocity. There must, therefore, be still another qualitative factor; this is that euglobulin has a higher valency, a greater intensity of antigen function than albumin. To be sure the euglobulin was greater in volume, but the albumin was used in optimal dosage. The animals sensitized in this way, after a favorable interval for the complete development of albumin hypersensitiveness, were reinjected, so that the antagonistic actions of the albumin and euglobulin ran counter to each other. The antigen function of nonoptimal doses of albumin can therefore be disturbed when the euglobulin given at the same time does not predominate in volume. Euglobulin and albumin function as antagonistic antigens, which proves anew that the differences in the albuminoids predominating in the individual fractions of a serum protein and giving it its distinctive character, are structural and chemical and not purely colloidal. It is not unimportant in the physiology of nutrition that the antibody-producing cells, when they are presented at the same time with 2 such closely related substances, make such a definite and certain choice.

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**The Colloidal Behavior of Serum Globulin.**

*David I. Hitchcock, J. Gen. Physiol., 5:35, Sept. 20, 1922.*

The author recalls Loeb's theory of the colloidal behavior of proteins. This theory is based on the idea that proteins are amphoteric electrolytes, reacting stoichiometrically with acids and bases to form ionizable salts, and on Donnan's theory of membrane equilibrium. The object of the author's investigation here reported was to determine whether the theory would explain the behavior of a serum globulin as well. The globulin prepared from ox serum by dilution and precipitation with carbon dioxide was found, by electrometric titration experiments, to behave like an amphoteric electrolyte, reacting stoichiometrically with acids and bases. The potential difference developed between a solution of globulin chlorid, phosphate, or acetate and a solution of the corresponding acid, free from protein, separated from the globulin by a collodion membrane, was found to be influenced by hydrogen-ion concentration and salt concentration in the way predicted by Donnan's theory of membrane equilibrium. The application of Loeb's theory of colloidal behavior may therefore be extended to another protein, serum globulin.

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**Action of Shaken Serum on Homologous Fibroblasts.**

*Alexis Carrel and Albert H. Ebeling, J. Exper. Med., 36:399, Oct. 1, 1922.*

An attempt was made to ascertain whether factors other than heat might bring about simultaneous changes in the inhibiting action of

serum on homologous fibroblasts, and in its alexinic activity. The purpose of these experiments was to study the effect of serum inactivated by shaking, on the growth of fibroblasts. Serum was obtained from the plasma of chickens about 1 year old, sealed in pyrex tubes, and shaken at low speed for periods varying from 1 to 8 hours. The lytic action of serum on foreign cells was ascertained with sheep corpuscles. Fibroblasts obtained from pure cultures of a 10 year old strain were used for measuring the effect of chicken serum on homologous cells. The medium consisted of 1 volume of normal plasma, 2 volumes of shaken serum, and 1 volume of shaken serum containing 1:20 embryo juice. In the controls, the shaken serum was replaced by normal serum. Five chicken serums and 3 fresh serums from dogs were subjected to examination, after being shaken for 1-8 hours. The serums were thus partly, rarely completely, inactivated as was shown by the hemolytic tests.

The experiments showed that partial or complete inactivation of serum by shaking brought about a marked decrease in the activity of homologous fibroblasts. Shaken serum always inhibited the activity of homologous fibroblasts more than normal serum. When chicken serum was completely inactivated by shaking, its restraining action on chicken fibroblasts became also more marked. On the contrary, dog serum partly inactivated by shaking was much less toxic for chicken fibroblasts than normal serum. Thus, shaking brought about a change in the condition of serum, against which homologous and heterologous fibroblasts reacted in an opposite manner. At the same time, the normal lytic action of serum on foreign erythrocytes decreased. This last phenomenon was caused by the partial or complete destruction of alexin. The decrease of the restraining effect of shaken serum on foreign fibroblasts may be attributed to the same cause. The increase of the inhibiting action of shaken serum on homologous fibroblasts is due possibly to the disappearance of a substance favoring the activity of homologous cells.

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**Serologic Tests with Antigens and Antibodies on the Surviving Perfused Spleen.**

*Martin Hahn and Emil von Skramlik, Biochem. Ztschr., Berlin, 131:315, Aug. 11, 1922.*

An anchoring of antibodies like antigens to the tissue cells was determined in numerous serologic tests. The bound bodies are only slightly affected thereby; agglutination of the respective bacteria occurs in the liver, in which bacterial agglutinins are held. The hemolytic amboceptors are capable of affecting the liver cells and the proper erythrocytes in spite of being anchored, resulting in increased agglutination, whereupon lysis appears in the organ after agglutination. The question was raised, whether this effect is peculiar to the liver, or whether it may result through other organs, as the spleen. It was shown that from the histologic standpoint the sheep spleen frequently behaves like the guinea-pig liver. Tetanus toxin is bound, but only its lytic components; the spastic hardly undergoes any diminution, whereas a distinct decrease was determinable in the liver. The spleen normally showed red cell amboceptors as well as agglutinins, which



were not demonstrable in the liver. This definite accord, in serologic aspects, between the hepatic and splenic function explains why the spleen can be readily dispensed with.

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**Availability of Extract Suspensions for Serodiagnostic Purposes.**

*F. Georgi, Klin. Wchnschr., Berlin, 1:1947, Sept. 23, 1922.*

The new method of Bruck for the serodiagnosis of syphilis is distinguished from the other flocculation reactions by the fact that previously suspended extract particles are held together, that is, there is agglutination, in contrast with precipitation of dissolved extract particles. The author has tested the heterogenetic flocculation of Forssmann's antigens by the Bruck method, especially the precipitation of alcohol-soluble antigens contained in the organs of guinea-pigs and horses, which are identical with the partial antigens of sheep blood, by suitable immune serums or by hemolytic sheep-blood antiserums. Of 160 cases, Bruck's reaction was in complete agreement with the Wassermann and Sachs-Georgi reactions in 148, and divergent in 12. In testing heterogenetic flocculation it was found that on the interaction of guinea-pig extract with sheep blood serum there was pronounced flocculation which was absent with cattle blood antiserum. The method is therefore adapted for heterogenetic flocculation. The reading can be done immediately after centrifuging the mixture. Bruck's method not only saves time but considerably increases the sensitiveness, as a tenth part of the immune serum is sufficient for a positive result.

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**On the Origin and Nature of Alexin (Complement) in Guinea-Pig Blood.**

*L. F. Morrison, J. Immunol., 7:435, Sept., 1922.*

In the author's experiments, the technic employed in obtaining guinea-pig blood and in titrating its alexin content was in all cases as nearly identical as possible. Normal male guinea-pigs were anesthetized with ether and the blood obtained by heart puncture. The blood was either allowed to clot, was defibrinated by agitation in a sterile flask containing glass beads, or was subjected to other treatment as demanded by the various experiments. In every instance, the pooled serum from at least 4 normal male guinea-pigs and in a few instances as many as 40 guinea-pigs was used in order that individual fluctuations in alexin content should not enter into the general considerations. In titrating the alexin content of each sample 2 series were set up, one series starting at a dilution of 1:2, the other starting at a dilution of 1:10. Subsequent dilutions of these were made in 0.85% NaCl solution, running in multiples of 2, resulting in dilutions of  $\frac{1}{2}$ ,  $\frac{1}{4}$ ,  $\frac{1}{8}$ ,  $\frac{1}{10}$ ,  $\frac{1}{16}$ ,  $\frac{1}{20}$  and so on to a point well beyond the anticipated titer limit. The hemolytic system employed was the usual rabbit serum-antisheep cell combination in which 3 units of the immune serum in 0.5 c.c. normal salt solution, 0.5 c.c. of a 3% suspension of washed sedimented sheep cells

together with varying amounts of reactivating substance in a total volume of 0.5 c.c., were employed. After the contents of the tubes were thoroughly mixed, the tubes were incubated for 30 minutes at 37° C. in a water-bath. Readings were made immediately after the tubes were removed from the water-bath and again after they had been allowed to stand overnight in the ice-box. The necessary controls were set up for each experiment. The author's studies embraced: (1) Quantitative determination of alexin. (2) Comparison of the alexin contents of clotted blood and plasma. (3) Reactivation of the alexin content of old guinea-pig serum. (4) The enzymatic nature of alexin.

The author observed that a far more powerful alexin, or complement, ready for immediate use, is obtained by the defibrination, centrifugalization and removal from the cells of guinea-pig blood serum than is obtained by the usual method of allowing the blood to clot and removing the serum after it has been allowed to stand on the clot for 24 hours. The same time and temperature relations as have been worked out for clotted blood-serum alexin, hold true for the defibrinated blood-serum alexin content. Concerning the leukocytic theory of the origin of alexin, the author believes it untenable. He presents experimental evidence showing the apparent inactivity of either the red or white blood-corpuscles to produce alexin, and also calls attention to the fact that blood plasma contains large amounts of alexin. The reactivation of old guinea-pig serum may be explained, the author says, by the enzymatic nature of alexin or by assuming that there are 2 thermolabile fractions of alexin, 1 being more susceptible to the detrimental effects of time and temperature than the other. The enzymatic nature of alexin is demonstrated by comparing the action of guinea-pig serum, high in alexin content, with the generally accepted reactions of pure enzymes: (1) by agitating the serum for a short time, producing a foam, and demonstrating that the foam has a greater alexin content than the fluid beneath it; (2) by the adsorption of alexin by foreign bodies offering a large contact surface; and (3) by its capability, under favorable circumstances, to act in dilutions greater than the calculated titer limit.

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#### **On the Photolability of Serum Complement.**

*E. G. Lundberg, J. Immunol., 7: 389, Sept., 1922.*

The purpose of this investigation was to discover the laws governing the destruction of complement (alexin) in normal serum by light. The complement used was exclusively undiluted normal swine serum. The blood was caught in sterile glass cylinders and left for 24 hours at room temperature; the serum was then decanted and frozen at about -14° C. and left so until required for use, when the bottled frozen serum was melted in water at about 25° C. and immediately afterward was put into an ice-bath until wanted for the experiments. For radiation the author employed a mercury-gas quartz lamp (from the "Quartzlampen Gesellschaft," Hanau) burning at 140-volt tension at the poles of the lamp and 4.3 amperes. The absolute light strength was never measured, but a constant range of 150 mm. distance was maintained between the lamp and the serum, when not purposely

varied in order to change the relative light intensity. The serum was exposed in a flat, round dish, with a bottom of mirrorglass and a frame of the same material, covered with a plate of Jena uviolglass, 1 mm. thick, 12 cm. in free diameter and giving a clear space of 4.5 mm. between the 2 glasses. The box was held together by picin and in the circular frame there was an opening 7 cm. wide for the insertion of a glass rod, acting as the mixer of the fluid, and for the filling and cleaning of the interior and also to allow of successive samples being rapidly taken out by means of a pipet. The dish never held more than 60 c.c. serum. The whole was immersed to two-thirds its depth in a water-bath with a motor-driven mixer, containing 30 liters, and was kept at a suitable constant temperature by means of a gas flame or a current of cold water. The temperature variations remained, as a rule, within  $0.10^{\circ}$ .

The mixing rod inside the serum holder was moved to and fro by the motor at the rate of about 20 oscillations per minute. As no foam was formed and the apparatus moved very gently, all destruction of complement by rocking may be regarded as excluded. The dish was fixed at an angle of  $45^{\circ}$ , with the surface of the water somewhat higher than that of the serum. The lamp was placed with its tube horizontal, parallel to the edge of the free serum surface and as near to this as possible. The distance was measured from the nearest point of the tube to the center of gravity of the front serum surface. The degree of accuracy for this distance may be estimated at 0.3 cm. Before radiating the serum in any experiment, the lamp current and the bath temperature were made constant. After this, serum was poured into the dish, which was then protected by means of an iron plate in front and a black paper behind, and the mixer started. A small quantity of serum (5 to 10 c.c.) was put into a Jena glass bottle in the same bath, light sheltered, as a control of the degree of destruction by temperature (heat control). After 10 minutes the iron plate was removed and the first sample was taken. After varying intervals, successive 2 c.c. samples were taken and, when higher temperatures were reached, control samples were taken now and then from the bottle. These samples were immediately put into an ice-bath, where they remained sheltered from light until titration. For the titration (which was performed at once or a few hours later) the method employed was a slight modification of that adopted by the State Serum Institute of Denmark, Copenhagen, for hemolytic measurements, as outlined in the Institute's "Communications" in 1909 and 1911.

A study of the detailed graphic, tabulated and mathematical data presented in the article shows that the light destruction may be fairly well expressed by the monomolecular formula. The rate of the destruction is low; the temperature influence is small or none. Variation in lamp distance causes changes in reaction speed, which do not differ essentially from inverse proportionality to the light intensity. Dilution of serum before radiating causes not only the expected decrease of complement strength, but also alters very irregularly its magnitude. It causes, too, an increase in reaction speed, which, however, is not parallel to the dilution amount. Regarding the accuracy of the measurements made with this method the primary figures have a possible error of about  $\pm 10\%$ , while the graphically found values have a possible error of about 5%.

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**Relation between Complement and Cholesterin Content of Blood Serum.**

*Harry Koenigsfeld, Ztschr. f. d. ges. exper. Med., Berlin, 29: 190, Aug. 19, 1922.*

The growth of typhoid bacilli in bile is not due exclusively to the action of the salts of biliary acids. The addition of bile inhibits the bactericidal properties of blood serum toward typhoid bacilli, manifested not only by a disturbance in the formation of antibodies but also by destruction of complement, so that the bactericidal substances are rendered ineffective; such destruction is conditioned on the cholesterin content of bile.

The author attempted to demonstrate experimentally in rabbits and guinea-pigs the variations in complement content of fresh serum with varying cholesterin content. A sheep blood amboceptor was prepared, using guinea-pig serum as complement, titrated with 5% sheep blood. In the experiment more than double the usual amount of amboceptor was used, to which were added varying amounts of the serum to be titrated for complement content, the volume of the latter being brought up to 0.5 c.c. by the addition of physiologic salt solution. With increasing cholesterin content there was gradual diminution in the complement to almost total disappearance. The complement is manifestly destroyed, either directly or (more probably) indirectly, being rendered ineffective by adsorption to cholesterin. In man, in carnivora and omnivora, all consumers of foods with high cholesterin content, the normal cholesterin content in the blood is rather high (0.1 to 0.2% in man); in herbivora, on the other hand, there is very little cholesterin but much more complement than in man. Hypercholesterinemia is found, pathologically, in inanition, chronic suppuration and abscess formation, with corresponding decrease—at times absence, of complement. Poisonous substances (as phosphorus and alcohol) that cause increased fat production and infiltration (hence lipemia), also cause diminution in serum complement; this is also true of substances like bile salts, which by their hemolytic and lipolytic action, liberate lipoid bodies and raise the total cholesterin content. Since elimination of cholesterin is effected by the liver, extirpation of the latter results in hypercholesterinemia and in total disappearance of complement.

In experimental pancreatic diabetes and the resultant lipemia, a similar disappearance of complement occurs. In paroxysmal hemoglobinuria, in intervals between attacks, the serum contains little or no complement. After exposure to cold there is reappearance of complement with relapse of hemoglobinuria. Injections of cholesterin render complement inactive and the attack is prevented, a result that may also be attained by a diet rich in cholesterin.

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**Effect of Hemorrhage on Complement of Blood.**

*Enrique E. Ecker and H. Maynard Rees, J. Infect. Dis., 31: 361, Oct., 1922.*

The effects of hemorrhage on the cellular elements of the blood are fairly well established. Within 10 minutes after hemorrhage the

leukocyte count begins to rise and reaches its height in a few hours, while an increase in platelets is seen during the first 24 hours, reaching a maximum within a few days. The red count is made up much more slowly than the others. The hemoglobin content is the last to return to normal. The fluid content is not fully made up until the third day. The relation between these changes and the complementing power of the blood has not been studied. It seemed desirable to ascertain the changes induced in complement by profound and multiple hemorrhages, and subsequent regeneration; and the relations, if any, of this change to the change in the cellular elements. Guinea-pigs were employed, and heart puncture was found to be the only practical method. The serum for titration was diluted 1:20, and an excess of amboceptor used. During the entire experiment the animals were fed on fresh vegetables but were given no fluids.

The first series showed that repeated small hemorrhages caused a mild chronic anemia, with a progressive increase of the mononuclear cells at the expense of the polynuclears in the differential count, but no constant or significant variation in complement. The second series reached a more profound anemia. Except for a slight drop in complement there were no changes attributable to hemorrhage, while the leukocytes and platelets behaved as in the first series. Apparently no appreciable or constant variation in the titer of the blood can be made out 24 hours after a hemorrhage even of great severity, and neither subsequent dilution nor any other event in the regeneration of the cellular elements affects the titer.

Further experiment showed that the titer began to drop 1 hour after a severe hemorrhage, remained low till the fifth hour and by the sixth hour reached normal again. Complement then has a regular curve of decrease and regeneration following a single severe hemorrhage, but is unaffected by subsequent dilution of the blood by body fluids. This curve does not follow that of any of the cellular elements and there seems no reason to believe that any of the cells is a factor in complement regeneration. The initial decrease in complement is due to blood dilution and the decrease is soon made up by an influx of complement from some unknown source.

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**The Action of the Visible Spectrum on Complement.**

*Enrique E. Ecker, J. Infect. Dis., 31:356, Oct., 1922.*

The inhibitory power of the invisible or ultraviolet rays on complement has received extensive recognition, and the bulk of this work has been done by direct exposure of serums to ultraviolet rays. It appears that no attempt has been made to study the effect of visible rays on complement and amboceptor. The present work was a study of the action of visible part of the spectrum on complement. Guinea-pig serums, whole, in 10% solutions, and dried were exposed to the rays of the visible spectrum, with controls. After the exposures, titrations were made using an antishoop amboceptor cell system. The results indicated that 3 hours' exposure had no effect on the serum, while from 6 hours on there was a gradually increasing inhibitory action, until after 29 hours the complement was practically destroyed.

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Diluted serum was more sensitive to the action of light than undiluted, while dried serum was much more resistant.

The experiment showed that the green-blue-violet end of the spectrum was considerably more active in destruction of complement than the red-orange-yellow end, but that the latter rays had some inhibiting action. The nature of light action on complement is still problematic, but it would seem to be purely chemical. Whatever the nature of the photosensitiveness of complement, light inhibits and destroys complement, and its action can be antagonized by the use of a member of the aromatic amino-acid series.

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**The Relation of Reduction of Leukocytes and Platelets to Complementing Power of Serum.**

*E. E. Ecker, B. S. Kline and A. DeCaluwe, J. Infect. Dis., 31: 368, Oct., 1922.*

The rôle of the leukocytes in the production of complement has been a matter of much study. The greater part of the work was done with no clear differentiation between amboceptor and complement, and by various methods of making extracts of white blood cells. The authors have attempted to reduce the number of circulating leukocytes in in vivo experiments, to find whether a parallel reduction of complement could be demonstrated.

Equal parts of benzene and olive oil were injected into rabbits subcutaneously in doses of 1 c.c. benzene per kilo of animal. The rabbits responded rapidly, and 3 or 4 injections brought the count of leukocytes below 1000 per c. mm. This, however, was not true of the platelets, as there was at times a slight increase. The complement titer in all instances remained within normal limits so that it seemed that the reduction in platelets and leukocytes in the circulating blood does not parallel the complement titer. The bone marrow and spleen of the treated animals showed serious deterioration as the result of the benzene; hence it would seem that these tissues are not important in any way in the maintenance of the complement of the serum. Observations of the authors seemed to indicate that there is an actual reduction in the number of circulating leukocytes rather than an accumulation in the dilated capillaries of the liver.

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**The Complement Effect of Serum-Free Organs. (Experiments on the Surviving Perfused Sheep Spleen and Sheep Liver.)**

*Emil von Skramlik and Otto Olsen, Biochem. Ztschr., Berlin, 131: 321, Aug. 11, 1922.*

The serum-free guinea-pig liver may act as complement to a hemolytic amboceptor. Although analysis of the processes in the organ shows 2 clearly distinct phases (first agglutination and organ fixation and then hemolysis), the process is indistinct in the test-tube. If an excess of complement be added to erythrocytes in a test-tube, with an

appropriate amboceptor in insufficient dosage for agglutination, in most cases dialysis appears immediately. Through dialysis, the complement may be separated into 2 elements—end piece and middle piece. Only their mixture acts hemolytically. On treating the serum of guinea-pigs with CO<sub>2</sub>, the middle piece goes over to the precipitate and the end piece remains in the fluid above it. If sheep cells in the presence of a hemolytic amboceptor in a concentration insufficient to produce agglutination are mixed with an amount of middle pieces, which in turn are incapable of agglutinating sheep cells, agglutination of the red cells soon appears. The middle piece promotes the agglutination of sensitized red cells. The middle piece must first be placed in the test-tube and after a certain interval the end piece of the sensitized red cells must be added. In this way it was shown that agglutination and organ fixation are produced in serum-free organs with the aid of the middle piece, and the final lysis is produced by the end piece. The aqueous extracts of serum-free sheep spleen contain the middle piece. Although in perfusion there is fixation of the sensitized red cells in the artificial circulation to the serum-free organ, a dissolution of these fixed red cells does not occur. The middle piece from the organ is given off to the red cells and upon this reaction the phenomenon of organ fixation rests. But no end piece is given off by the spleen in amount sufficient for hemolysis and the erythrocytes are dissolved only by the artificial administration of end piece to the fixed red cells through the circulation. The sheep liver behaves in a similar way; it has abundant amounts of middle piece but only slight amounts of end piece.

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**The Complement Fixation Reaction of the Cerebrospinal Fluid with Besredka's Antigen.**

*Fernand Arloing and L. Langeron, Rev. de la tuberc., Paris, 3: 434, Aug., 1922.*

The authors employed the method of Calmette and Massol in the study of 11 cerebrospinal fluids. Positive reactions with Besredka's egg antigen may be obtained in the entire absence of tuberculosis. The general fixation power of the antigen is greater than that of syphilitic antigen, but its significance is practically the same. Besredka's reaction and fixation with syphilitic antigen agree in 72.7% of the cases.

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**A Study of the Precipitin and Complement Fixation Reactions with Tuberculous Exudates, with Special Reference to Tuberculous Pleuritis.**

*Isamu Ogawa, J. Immunol., 7: 423, Sept., 1922.*

This investigation was undertaken to determine whether the immunologic reactions of precipitation and complement fixation occur with pleural exudates of tuberculous origin, as additional means and aids for the differential diagnosis of pleural effusions. Pleural fluids

were obtained from patients with tuberculous pleuritis, pneumococcus pleuritis, cardiac insufficiency with pleural transudates and from 1 case of carcinoma of the pleura with effusion; also from a large number of guinea-pigs and rabbits with experimental tuberculous pleuritis previously described by Kolmer and Ogawa. Precipitin tests were conducted with pleural fluids as precipitinogens and tuberculosis-immune goat and calf serums. The complement fixation tests were conducted according to the technic of Dr. Kolmer's new method for bacterial complement fixation tests. Each human and experimentally produced exudate was also studied bacteriologically, cytologically, and for albumin content.

The author found that in a series of 12 tuberculous pleural exudates, 42% yielded weakly positive precipitin and 92% well defined positive complement fixation reactions. Human pleural exudates and transudates of nontuberculous origin yielded uniformly negative precipitin and tuberculosis complement fixation reactions. In syphilis, however, positive reactions may occur due to the presence of reagin in the exudate unless precautions are taken to remove the lipoids from the antigen of tubercle bacilli. With the pleural exudates secured 15 days or longer after experimental tuberculous pleuritis in guinea-pigs, 8% yielded weakly positive precipitin reactions and 89% strongly positive complement fixation reactions. In experimental tuberculous pleuritis and pericarditis of guinea-pigs and rabbits, precipitins and complement fixing antibodies are not usually found earlier than 12 days after infection.

The author maintains that these results indicate that in the exudates of tuberculous pleuritis, precipitins and especially complement fixing antibodies, are found in a large percentage and that a sensitive complement fixation test with special attention to certain technical features, may prove a valuable practical aid to diagnosis.

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#### **Specific Precipitin Reaction of Leukocytes.**

*Ludvig Hektoen and F. R. Menne, J. A. M. A., 79: 1328, Oct. 14, 1922.*

The results of some experiments on the specific precipitinogenic action of leukocytes are briefly reported. The first experiments were made with extracts of dog and guinea-pig leukocytes obtained from the injection of suspension of wheat gluten in the pleural or peritoneal cavity. Later, attention was turned to human leukocytes. It is of interest to note that the antiserum of rabbits injected with human leukocytic extract did not contain any precipitin for the proteins in human serum. Extracts of dog, guinea-pig and human leukocytes were found to contain specific precipitinogenic substances. Whole human leukocytes and the serum of pleural exudate in empyema, also induce the formation of specific precipitins for extracts of human leukocytes. Leukocytes appear to contain specific elements not found in red corpuscles, platelets or blood serum, and these elements may be present in the serum of inflammatory exudates. No effort has been made to study the precipitin reactions of any special kind of leukocyte.

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**Polarimetric Researches on Serums and Their Bearing on the Wassermann Reaction.**

*P. Rondoni, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34:416, Aug. 25, 1922.*

Abderhalden, in connection with an article on the use of the polarimeter in biologic studies, maintains that the determination of the rotation of the plasma under different circumstances must lead to definite results. This immediately suggests the different infections and metabolic disturbances, especially diabetes. The author, in a series of polarimetric observations on human serum with reference to the reaction strength in the Wassermann test, found that the positive serums show a higher polarimetric value than the negative. The serum contains different substances with optical activity and the greater part of the known serum effect on polarized light is due to the serum albumin. The albuminoids in aqueous solution rotate polarized light to the left; only hemoglobin and nucleoproteids rotate it to the right. Besides the globulins, other substances in the Wassermann positive serums show rotating characteristics.

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**Wassermann Test Tube and Pipette Washer.**

*C. E. Swanbeck, J. Lab. & Clin. Med., 7:754, Sept., 1922.*

The apparatus was made from 2 nickel-plated brass tubes, which previously had served as towel racks. Ten small holes were drilled in each tube. The distance between each hole was made to correspond to the distance between the test-tubes in the Wassermann rack. A 5 in. length of copper tubing with a  $\frac{1}{4}$  in. outside diameter was inserted in each hole and soldered in place. The 2 brass tubes containing the copper tubing were now united at each end with pipe couplings and held apart so that the copper tubes were in the same relationship to each other as the holes in the Wassermann racks. At one end was inserted a pipe fitting to be attached to the general water supply pipe in the sink. To reinforce the copper tubing a wooden strip was inserted between the 2 rows, and a narrow strip of copper tacked on in such a way that it held the copper tubing against the wooden strip. When a rack containing the Wassermann tubes is now attached to the above apparatus and the water turned on, the tubes are thoroughly washed and cleaned in 10 minutes. They are then placed in distilled water to soak before drying and sterilizing. By attaching short strips of rubber tubing to the ends of the copper tubing one can insert the serologic pipettes into the rubber tubing and wash these in a similar manner. Twenty pipettes can be washed at one time on each washing outfit.

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**Kottmann's Silver Iodid Method.**

*Ernst Lauda, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 4:455, Aug. 25, 1922.*

By photochemical methods Kottmann showed that different serums varied markedly in dispersion activity on colloidal silver iodid. Into

the test serum colloidal silver iodid is introduced; this is exposed to light and is then developed by adding hydrochinon. The dispersion activity of the serum is judged from the intensity and rapidity of appearance of a brown coloration of the photosensitive silver iodid. According to Kottmann, various pathologic conditions of the thyroid are characterized by a difference in the serum colloids, that is, the dispersion effect on iodine substances shows recognizable differences. Bauer and Schur, in studies on hemoclastic crises, found that the brown coloration appears more quickly and more deeply in a serum inactivated at 55° C. for ½ hour, than in the active serum. The outcome of Kottmann's experiment is influenced by the chemical nature of the silver combination, the binding substance, the excess of silver nitrate, the presence of oxygen, the intensity of the light, duration of exposure and the strength and kind of developer. The author's research supported the assertion of Schur and Bauer that inactive serums generally react more markedly, but quite a few exceptions were found, especially in carcinoma serums. This is not yet clearly explicable. The complement content of the serum does not determine the character of the reaction. As to struma and serum in Basedow's disease, more material is required for proof.

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**A New Apparatus for Obtaining Serum for Biologic Tests.**

*Aul Dessy, Rev. Sud-Am. de endocrin. etc., Buenos Aires, 5: 317, Aug., 1922.*

One of the greatest difficulties in laboratory experiments is that of obtaining absolutely sterile serum. The usual tubes are fragile and difficult to sterilize. Dessy suggests an apparatus entirely of glass, in one piece, which can be sterilized with ease in the autoclave or by boiling water or physiologic solution, and which can be easily washed. The coagulum and serum can be readily kept separate, without danger of their mixing during transportation. The tube does not break easily, and its cost is moderate. The apparatus consists of 2 parts: an inferior portion containing a white bronze or brass spiral, which receives the blood and immobilizes the coagulum, and a superior portion for the serum. The inferior portion is a cylindric tube 2 cm. in diameter, with a U curve in its lower segment, the curved portion tapering down to a diameter of 8 mm. The upper, broad portion of the U forms a cone cut by a sloping facet. The superior portion of the apparatus fits over the cone like a cuff, is closed at its apex, and has a small ampuliform dilatation to catch the red blood-cells which may enter with the serum. It also has a small lateral tube for the passage of the serum.

With a sterile dry syringe, 3-5 c.c. blood are withdrawn from a vein in the axilla and placed in the inferior, narrow portion of the U, which is corked. With the tube slanted, a needle is introduced, and the blood is made to run into the internal portion of the tube. The blood is allowed to coagulate so that the coagulum is in the broad portion of the curve. After 1 or 2 hours the apparatus is inverted and held immobile. The serum runs into the cone and drops from the slanted apex into the receptacle, the coagulum remaining behind; the red blood-cells in the serum are collected in the ampuliform dilatation. The serum can then be poured into a sterile tube; it should be left in the apparatus until it reaches the laboratory, to avoid contamination.



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**Mastic Reaction of Blood Serum.**

*Karl Bauer and Paula Eder, Ztschr. f. d. ges. exper. Med., Berlin, 29: 246, Aug. 19, 1922.*

In all interreactions between proteins and colloidal solutions it has been noticed that solutions containing an excess of protein precipitated colloidal gold by flocculation. The authors employed the technic of Jacobstahl and Kafka to test the effects of the mastic reaction on blood serum. In 82 serums there was found to be a fairly definite distinction between syphilitic and nonsyphilitic serums. The former (with positive Wassermann) gave optimum precipitation and clouding reactions occupying a position about midway in the series.

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**Studies of Gas and Electrolyte Equilibria in Blood. I. Technic for Collection and Analysis of Blood, and for Its Saturation with Gas Mixtures of Known Composition.**

*J. H. Austin, G. E. Cullen, A. B. Hastings, F. C. McLean, J. P. Peters and D. D. Van Slyke, J. Biol. Chem., 54: 121, Sept., 1922.*

In the authors' experiments gross losses of  $\text{CO}_2$  were avoided by drawing the blood under oil in cylinders arranged as described by Van Slyke and Cullen. When oxalated blood was desired, potassium oxalate of tested neutrality was placed in the receiver in the proportion of 0.3 gm. to 100 c.c. of blood. When defibrinated blood was required the oxalate was omitted, and the blood was defibrinated by stirring under oil with a rod. The blood was then filtered under oil through gauze. The collection and centrifugation of blood for analysis necessitated the use of a special apparatus. In the saturation process, 2 methods were used to bring blood into equilibrium with gas mixtures of known composition. In both of them measured volumes of the gases were introduced into tonometers, which were then revolved in a water bath at  $38^\circ \text{C}$ . until equilibrium was attained.

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**Studies of Gas and Electrolyte Equilibria in Blood. II. The Reversibility of the Effects of Changes in  $\text{CO}_2$  and  $\text{O}_2$  Tensions on the  $\text{CO}_2$  Content of Defibrinated Horse Blood.**

*John P. Peters, Glenn E. Cullen and J. Harold Austin, J. Biol. Chem., 54: 149, Sept., 1922.*

Haggard and Henderson have stated that when the  $\text{CO}_2$  tension of dog blood, either defibrinated or oxalated, has been reduced to less than about 20 mm., the blood undergoes an irreversible (or at least not readily reversible) change, characterized by a diminution of its  $\text{CO}_2$  capacity. When this blood was again brought into equilibrium with a gas mixture with a higher  $\text{CO}_2$  tension it took up less  $\text{CO}_2$  than before its exposure to the low  $\text{CO}_2$  tension. This irreversible change was found more consistently in defibrinated than in oxalated blood. To determine whether such an irreversible change occurred in defibrinated horse blood, experiments were performed that reduced the

CO<sub>2</sub> tension of defibrinated horse blood to as little as 15 mm., but no irreversible change in the CO<sub>2</sub> capacity of the blood was produced. It seems likely, the authors maintain, that the irreversible fall in CO<sub>2</sub> capacity observed by Haggard and Henderson was due to the acid formation which is very rapid in dog blood.

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**Experience with Bang's Micro-Analysis.**

*Ludwig Petschacher, Biochem. Ztschr., Berlin, 131:116, July 29, 1922.*

Micro-analysis makes it possible to determine the chlorid, sugar and nitrogen content of a few drops of blood. Determination of chlorids is simplest, but the recognition of the change in color, despite the advantage offered by the insolubility of potassium chromate in alcohol, requires some practice. The determination of blood sugar by the current method is not accurate and gives information only if there are large variations in blood sugar. The rest nitrogen determination is not yet accurate.

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**A Micromethod for the Quantitative Determination of Acetone and Oxybutyric Acid in the Blood without Puncture of the Vein.**

*Alfred Lublin, Klin. Wchnschr., Berlin, 1:1748, Aug. 26, 1922.*

With a capillary pipet 0.2 c.c. blood is taken from the fingertip and put in a centrifuge tube containing 0.8 c.c. water, 0.3 c.c. 0.66 n. sulphuric acid and 0.3 c.c. 10% sodium tungstate solution being added for dealbuminization; the mixture is shaken, closed and centrifuged actively for 1½ minutes. The filtrate is poured into a Widal tube, and 0.75 c.c. of the filtrate with 0.09 c.c. blood are put into a 50 c.c. micro-Kjeldahl flask, and 25 c.c. water, 1 c.c. 10% acetic acid and a trace of talcum added to it. This is then distilled 10 minutes with a low flame and put in a 100 c.c. Erlenmeyer flask with 15 c.c. water, 5 c.c. 0.005 n. iodine solution and 2 c.c. 25% caustic soda. Then to another portion of the filtrate prepared in the same way and without changing the flame, 20 c.c. potassium bichromate sulphuric acid is added drop by drop and after 10 minutes the distillation is stopped. Each portion is acidified with 2 c.c. 25% sulphuric acid and titrated with 3 drops each of 1% starch solution and 0.005 n. sodium thiosulphate solution. The entire determination takes 30 minutes.

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**Determination of the Urea Content in Small Quantities of Blood.**

*T. J. J. H. Meuwissen and R. L. J. van Ruyven, Nederl. Tijdschr. v. Geneesk., Haarlem, 66:1264, Sept. 16, 1922*

The authors employed McLean's graduated pipet. If completely free of grease this may be accurately filled with blood. In testing with Bahlmann's method, foaming was prevented by using 1 drop of

Kahlbaum's normal octyl alcohol. Foaming may break the fragile tube which receives the blood. The tubes employed were globular above and closed by a rubber stopper with 2 perforations to admit tubes, one for air and the other for discharging air. The receiving tube hung down to the bottom of the tube, bearing a bulb with fine openings. The discharge tube was slightly expanded to avoid splashing.

An apparatus was arranged to hold 9 pairs of tubes so that the blood tubes rested in a water bath kept at  $37^{\circ}$ . One tube received 4 drops 1% potassium oxalate solution and 0.2 c.c. blood, the pipet being then rinsed with 0.6% solution primary potassium phosphate. This salt prevents the production of an alkaline reaction, opposing the action of the urease, which would otherwise occur on account of the decomposition of the urea. Six drops of a fresh solution of soy-bean urease were then added. After mixing, the tube was incubated for 45 minutes at  $37^{\circ}$ . The other tube of the pair received 2 c.c. of 0.02 n. HCl and a drop of amyl alcohol. After incubation, 20 drops saturated NaOH solution and a drop of octyl alcohol were added to the blood tube. Air was then vigorously sucked through the blood for 50 minutes, by the aid of 2 wash-bottles containing dilute sulphuric acid. It was then passed through the HCl tube and through two check tubes containing no urease. Free acid was then titrated, the indicator being iodine liberated from potassium iodide and potassium iodate and used with starch. The difference between the 2 acid tubes was compared with the ammonia derived from the blood urea. This method is exact and only half the quantity of blood necessary for Bahlmann's method is required.

The authors modify the Folin-Wu method by placing 0.2 c.c. blood in a glass-stoppered measuring tube holding 5 c.c. The pipet is twice rinsed with water. Then 0.5 c.c. of the urease solution is added to the measuring tube, which contains blood and 0.1 c.c. water, and 2.9 c.c. water is added and the whole is mixed. As 1 c.c. water is used to wash in all the blood, the total volume is 4 c.c. The mixture is incubated for 30 minutes at  $40^{\circ}$ , 0.5 c.c. of 10% sodium tungstate solution and 0.5 c.c. of 0.66 n. sulphuric acid are then added and the mixture is vigorously agitated for 5 minutes. Of the filtrate, 3 c.c. is placed in a long-necked flask and 2 c.c. saturated solution of borax are added. The flask is closed with a rubber stopper admitting a tube bent into two loops and passing to the bottom of a reagent tube also stoppered with rubber and admitting air. Half the liquid is distilled and collected in the reagent tube, containing 2 c.c. of 0.06 normal HCl, the tube being cooled in water. The conveying tube is rinsed before making the colorimetric determination with Nessler's reagent. Turbidity may be avoided by agitating the distillate and adding an equal volume of reagent diluted in an equal volume of water, 2.5 c.c. of each. The volume is then made up to 25 c.c. A standard solution containing 0.075 mg. N per 100 c.c. is prepared with ammonium sulphate. This corresponds, in milligrams of urea, with 0.075 multiplied by 60.12 and divided by 28.08. The calculation is simplified since the 3 c.c. filtrate is derived from two-thirds of 0.2 c.c. blood. A little ammonia may be formed from substances in the albumin-free filtrate. Two determinations may be made, with and without urease, for checking. The final figures for 100 c.c. blood must be multiplied by 500. Residual nitrogen was determined by removing albumin with sodium tungstate

and sulphuric acid. The methods described are much more exact than the hypobromite method. The protocols are tabulated.

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**Note on the Reliability of the Benedict and Folin-Wu Blood Sugar Determinations.**

*F. A. Csonka and Grace C. Taggart, J. Biol. Chem., 54: 1, Sept., 1922.*

The authors made comparative studies of the Folin-Wu method and Benedict's picric-picrate method of blood sugar determination on the blood (taken before breakfast) of normal and diabetic subjects, and tabulated the blood sugar in milligrams per 100 c.c. blood. They employed the Folin-Wu method and the Benedict technic applied to the tungstate filtrate and the picric-picrate filtrate. The results show that the Folin-Wu blood sugar determination gave more reliable results than Benedict's picric-picrate method.

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**Determination of Occult Blood by a Quantitative Method.**

*Julius Gattner and Emma Schlesinger, Ztschr. f. klin. Med., Berlin, 94: 426, June 30, 1922.*

The benzidin method is perfectly adaptable for quantitative estimation of occult blood for clinical purposes and is easily carried out. Two grams of feces are thoroughly macerated and mixed with 8 c.c. distilled water in a porcelain dish. A series of test-tubes (about 10) are set up, each receiving 2 c.c. distilled water, the first tube alone remaining empty. Into the first and second tubes 2 c.c. of the feces emulsion is placed and is well shaken to prevent sedimentation. Tube 2 contains, therefore, a mixture of 2 c.c. distilled water and 2 c.c. feces emulsion. From this tube, 2 c.c. is placed into Tube 3 with a small pipet. After this mixture has been well shaken, 2 c.c. is transferred to the next tube, and so on, until the last tube contains 4 c.c. of fluid. This last tube is not used in the test, but is kept for further dilution in case the blood content of the sample is large enough to require this. The reagent is prepared with 10 c.c. of 10% benzidin solution in glacial acetic acid, 2 c.c. perhydrol, 8 c.c. of 0.1 n. sulphuric acid and 10 c.c. distilled water. Of this reagent (well mixed), 3 c.c. is added to each of the tubes. If the blood content of the feces under examination is high a positive reaction will be obtained in the tube containing the highest dilution; with moderate amounts of blood in the sample even the first dilutions may be negative. In order to determine the lowest amount of blood sufficient to give a positive reaction, the authors prepared a powder from blood obtained from abattoirs. The lowest quantity of this powder giving a positive reaction is 0.8-0.9 mg. in 100 c.c. distilled water; 0.7 mg. in 100 c.c. distilled water gave uniformly negative reactions, whereas 0.9 mg. in a like dilution was distinctly positive. The amounts of blood powder in 100 c.c. distilled water necessary for a positive reaction varies from the first to the eleventh tubes, respectively, as follows (milligrams): 0.9-1.8, 1.8-3.6, 3.6-7.2, 7.2-14.4, 14.4-28.8, 28.8-57.6, 57.6-115.2,

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115.2-230.4, 230.4-460.8, 460.8-921.6, and 921.6-1843.2. If the reaction is positive only in the first tube, the reading is 0.9 mg.; if up to the seventh tube the reading is 57.6, and with a positive reaction in the twelfth tube the figures are 1843.2 mg. for each 100 c.c. of excrement. Where the findings in the same case are positive on one day to the fourth dilution and on the next day in the fifth dilution, this does not necessarily indicate an aggravation of the condition. The total blood content—the original feces being diluted with 4 times the volume of water in the fifth glass—has simply risen from 5 times 7.2 mg. to about 5 times 14.4 mg. blood powder in each 100 c.c. feces. If, on the other hand, a reaction that has been positive to the tenth dilution becomes positive also in the eleventh, the actual rise in blood content of each 100 c.c. feces is tremendous—from about 5 times 461 mg. to about 5 times 922 mg. The difference in the latter case is so great as to justify serious apprehensions as to the course of the disease.

This method records the fluctuations of occult bleeding in a manner not possible by any other procedure and serves as a guide to therapy. It is important that the glassware and other containers be absolutely free from blood traces and that the blood in the feces is fairly evenly distributed.

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#### **Clinical Determinations of the Amount of Blood.**

*Herzfeld, Münch. med. Wchnschr., 69:1272, Sept. 1, 1922.*

The author has made a series of experiments with the method recommended by Griesbach for determining the amount of blood. The method is briefly as follows: A 1% solution of Congo-red is prepared with distilled water and 10 c.c. are injected intravenously into the person to be experimented on. Four minutes after the injection about 10 c.c. of blood are taken with the syringe. This is defibrinated and then the proportion of serum and blood-platelets determined with the hematocrit or strong centrifuging. The pigment content of the reddish colored serum is then determined with an Authenrieth's colorimeter. A 0.01% solution of Congo-red in distilled water is used as a fluid for comparison. From a curve graduated for the stain in question, the degree of dilution of the Congo-red in the serum can be determined. From this the total amount of blood is calculated taking into consideration the volume per cent. of the corpuscles into which the stain does not enter. The method is entirely harmless as the author has shown by 60 experiments, and is also comparatively easy to perform. The determination of the total amount of blood by the injection of stains is a useful clinical method, but it is doubtful whether absolutely correct values are obtained. It seems, however, that usable comparative values can be obtained, and in this way many questions can be answered with more certainty than has hitherto been possible.

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#### **The Ion Exchange between the Blood-Corpuscles and the Serum.**

*Klothilde Meier, Klin. Wchnschr., Berlin, 1:1748, Aug. 26, 1922.*

The ion exchange between the serum and the blood-corpuscles is dependent on the reaction of the blood. By the introduction of carbonic



acid into the blood, the carbonic-acid combining capacity of the serum and its alkali content increases, while its chlorin content decreases by migration of chlorin into the corpuscles; in this process, the amount of alkali set free is less than that necessary for the carbonic-acid fixing. This alkali deficit is probably covered by a migration of alkali from the blood-corpuscles into the serum. At the time of the ion migration, water flows out of the serum into the blood-corpuscles and their volume increases as the density of the serum increases.

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**The Blood-Cells of Certain Lamellibranchs.**

*L. M. Betances, Arch. d'anat. micr., Paris, 18:309, Aug. 15, 1922.*

The author has studied the blood-cells of *Cardium edule*, *Mytilus edulis*, *Pecten maximus* and *Littorina littorea*. The technic, including staining with May-Grünwald panchrome, was described in the 1921 volume of the *Arch. d'anat. micr.* The blood-cells of the mollusks examined are analogous with microlymphocytes, plasma-cells, monocytes and hemocytoblasts of mammals. Among them are also cells resembling Türck cells and Rieder cells, mature microlymphocytes with fusiform cytoplasm, glandular cells and bare nuclei. The granular cells of these mollusks are like those of crustaceans, being amphophil, with rhagiocrin secretion. All phases are represented by the same forms as those of crustaceans (granulocytoblasts, granulocytes and rhagioplasts), except that the secreted substance sometimes stains almost black. These cells are thus both eosinophilic and sitistocytic. The secreted substance often reacts like mucin. It undergoes various transformations. Granulation is largely effected by the spongioplasm. The morphogenesis is the same as that of crustaceans. It is sometimes difficult to differentiate true, mature lymphocytes from old, free epithelial cells. The very diffuse leukopoietic tissue of lamellibranchs is composed of connective and endothelial tissue and Cuénot's lymph organs. The function of the blood-cells is the same as that of leukocytes in general. However, their chemotaxis is limited, and only certain of the cells are phagocytic.

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**The Structure of the Erythrocytes; Their Membranous Envelope.**

*Petru Galesescu, Spitalul, Bucharest, 42:201, July-Aug., 1922.*

The author's investigations are based on colloidal chemistry, observations being made with a Zeiss' cardoid-condensor on erythrocytes that had been subjected to the action of different hypotonic and hypertonic solutions, as well as other hemolytic procedures. It was found that hemolysis is the result of 2 or 3 substances which form the membrane of the erythrocytes: (1) a network formed of protein bodies, (2) lecithin, and (3) cholesterin. The stroma of the erythrocytes is a solution of hemoglobin rich in salts. The author calls this endosoma. From his own experiments and those of others he concludes that the erythrocytes are not enveloped in a membrane in the anatomic sense, but only in the physical sense.

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**The Marginal Band in Human Erythrocytes.**

*Petru Galesescu, Spitalul, Bucharest, 42:205, July-Aug., 1922.*

The author succeeded in staining and isolating the marginal band in human erythrocytes. The technic is as follows: A drop of blood is put on a slide and over it a drop of 3-5% solution of sea salt; these are well mixed and covered with a cover-glass. As soon as it can be seen through the microscope that the blood-cells are changing in the hypertonic solution, a drop of saturated alcoholic solution of crystal violet, filtered just before using, is put under the cover-glass, as in Gram's method. Then it is examined with the immersion lens, and a circular violet band is seen which gradually becomes more pronounced, and sometimes wavelike. On the inner side of it points can sometimes be seen, as if the band were punctate. If the hypertonic solution has acted for a long time, the bands become separated from the cell and can be seen lying free in the field. Permanent dry specimens can be made if the specimen is dried after being treated with the hypertonic solution. They are then fixed with alcohol and stained with iron-hematoxylin. Romieu's gold-chlorid method does not give good results. The examinations were made on normal blood, on hemorrhagic lumbar punctate, in hemorrhagic nephritis, on leukemic blood, in severe anemias, etc. In all these conditions the marginal band was visible. The author concludes from this that the marginal band is present in man in normal as well as pathologic conditions. Its object is to preserve the normal form of the erythrocyte by its elasticity.

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**The Influence of the Spleen on the Red Blood-Cells.**

*N. A. Bolt and P. A. Heres, Klin. Wchnschr., Berlin, 1:1795, Sept. 2, 1922.*

In the determination of the osmotic resistance of the blood-cells from the splenic vein in comparison with those from an artery, the method must be changed, as the isotonic sodium chlorid solution which has heretofore been used for the washing of the blood-cells exercises a liquefying action on the surface of the erythrocytes and so may cause hemolysis. The authors, therefore, use hypotonic equilibrated solutions (calcium-containing, modified Ringer's solution). They find great decrease of resistance of spleen blood-corpuscles as compared with carotid blood-corpuscles. By washing with equilibrated salt solution, a hemolytic substance (phosphatid) is washed from the surface, which is always inhibited by the cholesterin of the corpuscles. The proportion of cholesterin to phosphatid determines the osmotic resistance of the erythrocytes. When the hemolytic function of the spleen lowers this proportion, after the washing out of this complex the 2 kinds of blood show a similar resistance. The spleen function may consist in lowering the resistance of all corpuscles that enter it; the weaker ones yield to the action completely while the stronger ones are only weakened by it. The same results are found in animals as in examinations of human blood from the splenic vein.

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**Further Observations on the Effects of the Subcutaneous Injection of Splenic Extract.**

*Ardrey W. Downs and Nathan B. Eddy, Am. J. Physiol., 62: 242, Oct. 1, 1922.*

The authors' experiments were performed on rabbits. In the first group there were 5 rabbits which received a daily dose of protein-free splenic substance, 10 mg. per kg. body weight, later increased to 20 mg. and finally to 40 mg. The dose of splenic material was dissolved in normal saline solution, 0.7%, while at the same time the control rabbits were given an injection of a corresponding quantity of normal saline solution. The weight curves and the white corpuscle count were observed to be parallel for the experimental and the control animals, but subcutaneous administration of protein-free splenic extract caused the occurrence of reticulated cells in the circulating blood in proportion much greater than normal as well as the appearance of nucleated red corpuscles in the rabbit's circulation. The resistance of the circulating red corpuscles was observed to extend over a wider range than normal. This resistance was determined by using solutions of chemically pure sodium chlorid in distilled water, ranging in strength from 0.550% to 0.150%, the decrease each time being by 0.025%; 1 c.c. of each solution was placed in a small test tube, a drop of blood added, the tube inverted to mix the blood and salt solution and the mixture allowed to stand for 24 hours. Then without disturbing the tubes they were examined and readings made of the tubes showing no hemolysis, partial hemolysis and complete hemolysis.

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**Blood Picture in Experimental Collargol and Salvarsan Poisoning. Contribution on the Genesis of Bone-Marrow Cells.**

*F. Herzog and A. Roscher, Ztschr. f. d. ges. exper. Med., Berlin, 29: 224, Aug. 19, 1922.*

Following salvarsan injections, under certain conditions a distinct change occurs in the blood picture equivalent to aleukemia and characterized by the disappearance of all granular elements in the leukocytes. A similar blood picture was noted after injections of collargol (experimental), the general nature of the blood changes being identical for the 2 preparations. The initial dose of each preparation was the normal therapeutic one, and was eventually increased to many times this dose.

Frank found, after intravenous injections of collargol, not an aleukemia but an anemia. If salvarsan was first administered the red cell count remained fairly constant, the white cells alone showing slight variations in number. A striking feature in the last cases was a rather high percentage of leukocytes with indistinct nuclei, the cytoplasm granules seemingly being washed out and staining very poorly. If collargol was then administered a progressive anemia set in, the leukocyte count increasing at the same rate as the normoblasts; among the white cells there were numerous granulocytes and occasional myelocytes. Later there was leukopenia, but without diminution of granulated elements as in aleukemia. Injections of salvarsan alone were not

followed by anemia; the red count remained unchanged, there were no normoblasts, the leukocyte count diminished very slightly. Nor were myelocytes found in any large numbers; toward the end of the experiment there appeared a few basophils. No aleukemia could be established.

Histologic examinations of the bone-marrow of animals fatally poisoned with neosalvarsan showed considerable increase in the number of cells, particularly of granular bone-marrow elements. In the animals poisoned with collargol a considerable portion of the bone-marrow was transformed into a new type of marrow, richer in connective tissue and more fibrous, exhibiting remarkable properties for the production of new bone-marrow elements, particularly very young basophil forms. In animals poisoned with both salvarsan and collargol the changes in the bone-marrow corresponded more to those after poisoning with collargol alone. The spleen of animals killed with collargol showed distinct myelogenous metaplasia, which was present in only moderate form in animals poisoned with salvarsan. The liver in the collargol group of animals showed areas of central fatty infiltration and necrosis, which were absent in the livers of animals in the salvarsan group; the latter only showed small hemorrhagic areas. Animals poisoned by simultaneous injections of both preparations showed the most pronounced central necrotic areas. In lymph-glands there was no abnormality beyond a substantial phagocytosis of interstitial cells and the endothelial lining of acini. The kidneys of animals killed with collargol showed fatty infiltration of the tubules and glomeruli to a greater extent than in animals dying after salvarsan administration.

The formation of new cells seemed to originate in the basophil elements of the bone-marrow, through the endothelial stages. There have also been observed smaller basophil stages in the formation of giant cells, the nuclear structure of which exhibited striking resemblance to myeloblasts. The long protoplasmic pseudopods (Wright), after being cast off, divided into very small platelets, within which definite round structures could be identified. Collargol thus caused grave degenerative parenchymatous changes, noticeable only faintly after salvarsan. The hemorrhagic areas observed after injection of the latter pointed to injury of blood-vessels in various organs. When both preparations were injected simultaneously the deleterious effects of collargol were exerted much more readily, the degenerative changes in the liver becoming considerably more pronounced.

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**Changes in the Physicochemical Structure of the Blood Due to Increased Erythrocyte Sedimentation Following Ingestion of Irritants, Surgical Procedures or Disease.**

*Wilhelm Löhr and Hanns Löhr, Ztschr. f. d. ges. exper. Med., Berlin, 29: 139, Aug. 19, 1922.*

Following the introduction of irritants into the body, as well as in the course of rapidly fatal diseases, there is a primary change in the equilibrium of the plasma proteins, especially of the fibrinogen fraction. The various plasma reactions, commonly understood to depend on the stability of the plasma, run parallel to the rate of sedimentation. The

various blood protein fractions possess different potencies for increasing agglutination, e.g. fibrinogen more than globulin, with albumin ranking next. So far as the fibrinogen fraction is concerned, during coagulation the precipitation rate was decreased; it is not certain, however, whether the original increase was due to fibrinogen or to some other component of the plasma that is abstracted and utilized in the formation of fibrin. Starlinger ascribes greater importance to the varying, quantitatively determinable fibrinogen content of the plasma, but Oettingen observes that the variation in fibrinogen content—if we recognize a physicochemical variability in the structure of the blood affecting its rate of dispersion—is merely the expression of the deleterious change occurring within the plasma. An increased rate of sedimentation is apparent even in the defibrinated blood of gravid women, though less pronounced. Thus the most vulnerable and least evenly distributed fraction, fibrinogen, cannot play the most important rôle in the production of the phenomenon but, as Fahraeus pointed out, there must be some parallelism between rapidity of sedimentation and globulin content.

The authors sought to determine the physical changes in the blood following injection of foreign proteins, in infectious diseases, and after surgical operations under aseptic conditions. The plasma flocculation reactions of Sachs and Oettingen were not used, but studies were made of the changes affecting viscosity, refraction and surface tension. The first change was an increase in the fibrinogen content; at the same time there was marked increase in the relative viscosity of the plasma, and this ran parallel with an increased rate of sedimentation and diminished surface tension. The highest relative viscosity invariably accompanied the greatest acceleration in sedimentation rate. These results were to be expected in disease. In pathologic states associated with marked protein decomposition an increased sedimentation rate uniformly accompanies increased viscosity of the plasma.

By the Naegeli-Rohrer method for determination of the albumin: globulin ratio there was noted regularly a variation of the formula toward the globulin side. Similar changes, although more moderate, were also noticed in the serum. The aseptic operations, owing to the constancy of the procedure and abundance of blood flow, proved the most reliable method of experimentation; single injections of foreign proteins yielded no consistent results. The graver the nature of the surgical procedure, the more pronounced were the changes in the physicochemical structure of the blood. Pharmacologic findings were inconclusive. Single injections of autogenous protein proved relatively nontoxic; histones and protamins were exceedingly toxic even in minute amounts, this being true also of bacterial proteins.

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### **Growth-Promoting Function of Leukocytes.**

*Alexis Carrel, J. Exper. Med., 36: 385, Oct. 1, 1922.*

The purpose of the experiments described in this article was to ascertain whether leukocytes contain and secrete growth-promoting substances, and whether tissues and exudates in which they accumulate acquire the power of activating cell proliferation. Leukocytes were

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obtained from the blood of chickens 1 or 2 years old. Their activity was tested against fragments of embryo chick heart and pure cultures of chicken fibroblasts. The medium was composed of 1 or 2 volumes of plasma and 1 volume of leukocytic extract. In the controls, the leukocytic extract was replaced by Ringer's solution or by embryonic juice. The rate of growth was ascertained by measurements of the width of the ring of new tissue which had grown in 48 hours. Fourteen experiments were performed, and results show that dead leukocytes set free substances which promote cell multiplication as do embryonic juices. In the same way, investigations were made as to whether living leukocytes may secrete growth-promoting substances such as are extracted from them after death. It was evident that, under the conditions of the experiments, leukocytes secreted a substance which activated the rate of growth of fibroblasts. If leukocytes be capable of setting free growth-promoting substances in vivo as well as in vitro, tissues and exudates where they accumulate must acquire the power of accelerating cell multiplication. Therefore, an attempt was made to ascertain whether inflamed connective tissue contains growth-promoting substances. In order that leukocytes could accumulate in inflamed connective tissue, a focus of aseptic inflammation was produced by injecting a solution of dilute HCl into fragments of sponge placed under the skin of chickens. Such inflamed connective tissue was found to contain substances capable of increasing the rate of growth of fibroblasts. Similarly, it was shown that a peritoneal exudate containing many leukocytes had acquired the power of stimulating cell multiplication.

Two main facts were brought to light by the preceding experiments: first, the presence of growth-activating substances in leukocytes; second, the setting free of these substances in tissues and exudates where leukocytes accumulate. The existence of growth-promoting substances within the body of leukocytes was to be expected. Leukocytes are embryonic cells and it is well known that embryonic tissues contain substances which stimulate cell proliferation. During the whole life and even in extreme old age, then, there is a supply of growth-promoting substances within the organism which is potentially capable of restoring the activity of resting cells.

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#### **Pure Cultures of Large Mononuclear Leukocytes.**

*Alexis Carrel and Albert H. Eberling, J. Exper. Med., 36: 365, Oct. 1, 1922.*

The purpose of this paper is to describe the characteristics of pure cultures of large mononuclear leukocytes, the morphologic changes of the cells, and their response to certain modifications in the composition of the culture medium. The blood of an adult chicken which had fasted for 24 hours was taken in cold paraffined tubes through an oiled cannula or syringe and centrifuged at high speed for 10 minutes. After removal of the plasma, a few drops of embryonic juice (diluted) were placed at the surface of the buffy coat of leukocytes; 15 minutes later, the coagulum containing the white cells could be removed and

placed in a watch-glass with a small amount of Ringer's solution. Several different mediums were used. In some experiments, no embryonic tissue juice was used and the medium was composed of plasma alone, or of plasma and Tyrode's solution. In other experiments, the medium consisted of 2 volumes of plasma and 1 volume of chick embryo juice, or of 1 volume of plasma, 1 volume of chick embryo juice, and 2 volumes of Tyrode's solution. Sometimes 20% fibrinogen suspension was substituted for the plasma. The culture medium was placed on a cover-glass of mica, and a small fragment of the leukocyte film was embedded in it before coagulation. Where the culture was properly prepared, a great number of ameboid cells were seen in the medium in 24 hours. After the first 24 hours, transfer into a fresh medium was made every 48 hours and even every third, fourth or fifth day. The first strain of large mononuclear leukocytes was kept in a condition of active life for almost 3 months.

After 24 hours, the fragment of coagulum containing the white blood-corpuscles was surrounded by a very large number of cells which sometimes invaded the entire area of the medium. The outer zone was made up of small ameboid cells. The inner zone consisted chiefly of larger ameboid cells. Some of them were very large and more or less elongated and branched, with reticular pseudopods. The others were smaller, more rounded in form, and emitted active filiform or lobar pseudopods. After 24 hours, fragments of coagulum containing the ameboid cells were extirpated from the cultures and placed in a new medium. The cells migrated almost immediately from the old into the new coagulum. The activity of the cultures was irregular. The migration of the cells from the edges of the old coagulum started from the first to the fourth day. The cells were usually disposed in chains which followed almost parallel paths into the new medium on several different planes, but every chain was laterally isolated from the others. The multiplication of the cells was slow. However, a few mitotic figures were observed. The general appearance of the cultures was strikingly different from that of a fibroblast culture. The cells had no tendency to form a tissue, but always remained isolated. The large mononuclear leukocytes invading the culture medium were almost uniform in shape, elongated or branched, and of irregular form. Their posterior end was generally rounded, while the anterior end emitted very active reticular pseudopods.

In actively growing cultures, the appearance of the cells remained uniform, as a rule. However, important morphologic changes sometimes occurred, generally when the migration and multiplication of the lymphocytes were not very active. The cells which showed the first evidence of a change were the elongated lymphocytes with clear cytoplasm and reticular pseudopods. The transition forms were apparently half fibroblasts and half ameboid cells. Sometimes the nucleus of an ameboid cell lost its character of being darkly stained by azure, and became pale and oblong with 2 nucleoli like that of a typical fibroblast. Typical macrophages were seen at the periphery of the culture and sometimes in the immediate vicinity of the transition forms and the fibroblasts. As with fibroblasts, the activity of the large mononuclears was found to be increased by embryonic tissue juice and inhibited by homologous serum when these were incorporated in the culture medium.

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**The Physiology of the Lymphoid Tissues.**

*F. Mas y Magro, Arch. de cardiol. y hematol., Madrid, 3:340, Sept., 1922.*

The effects of injections of adrenalin, pilocarpin, atropin, gland extract and a mixture of gland extract and pilocarpin were examined in dogs, rabbits and guinea-pigs. The early effects of adrenalin appear in 2 phases, occurring, respectively, 30 and 60 minutes after injection. The blood-count for the peripheral blood is not identical with that for the heart blood and blood of the great vessels. In the capillary blood, slight polycythemia and increase of leukocytes occur in the first phase, slight oligocythemia and leukocytosis in the second. The leukocytes and red cells tend to diminish, in both phases, in blood taken from the heart and larger vessels. If gland extract be added to adrenalin, it prevents the changes in peripheral blood otherwise produced by adrenalin. Lymphocytosis occurs in the first, increase of neutrophils in the second, adrenalin phase, whatever the source of the blood. A mixture of gland extract with 2-3 times the usual lethal dose of adrenalin proved practically harmless, never causing grave intoxication or death. In the capillary blood, the mixture produced increase of neutrophils in both phases. In the blood of the heart and larger vessels, it caused lymphocytosis in the first phase, increase of neutrophils in the second. The adrenalin lymphocytosis is thus unaffected by gland extract. It also occurs in splenectomized animals. In animals previously treated with lymphatic-gland extract, adrenalin produced diminished lymphocytes, whatever the source of the blood. In the circulating blood and blood-forming tissues, adrenalin diminishes the macrolymphocytes, Kurloff bodies and eosinophils.

**1f. PATHOLOGY**

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**The Question of Inflammation and Histophysics.**

*R. Thoma, Virchow's Arch. f. path. Anat. etc., Berlin, 238:366, Aug. 14, 1922.*

The symptomatic definition of inflammation (of Marchand, Thoma, Lubarsch) has the advantage of being demonstrable, but nevertheless does not take into sufficient account the great variability of the cases. The teleologomechanical conception of inflammation (Neumann, Aschoff, Marchand) also appears to be irrelevant. The purely etiologic definition is as follows: The conception of inflammation includes the local, reactive processes appearing at the site of the abnormal action as physical, chemical and infectious etiologic complexes. In a complicated fracture, for example, it is shown how arbitrary the separation into inflammatory or reactive and regenerative processes is. In addition the teachings of the theory of irritation are attacked. The principle of inflammation is an attempt to bridge the chasm between cause and effect, and many unsolved questions concerning it still remain. On the basis of all these considerations, Thoma deems it best to abandon that conception of inflammation which has frequently misdirected the investigation from the purely inductive path. By way of

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inductive investigation, histophysics might answer a part of those questions which the conception of inflammation has attempted to answer with theories.

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**Absorption Properties of Normal and of Inflamed Mucous Membrane of the Mouth. The Physiochemistry of Inflamed Tissues.**

*E. Hauberrisser, Ztschr. f. d. ges. exper. Med., Berlin, 29:200, Aug. 19, 1922.*

The problem of inflammation resolves itself, according to Cohnheim, primarily into a pathologic change of the blood-vessels, whereas Virchow conceives inflammation as a functional change of tissues in the sense of heightened physiologic activity. Experiments performed by the present author showed that inflamed tissues exhibited diminished absorptive properties when exposed to all manner of absorbable fluids as compared to normal tissues of the same animal. With respect to absorption, in spite of identical histologic conditions, various portions of the buccal mucosa seemed to react differently. One is almost forced to assume the existence of a functional, or at least physicochemic, differentiation of the various portions of the mucous membrane of the mouth. The mucosa covering the palate seemed to exhibit the lowest absorptive property, followed in an upward direction by the lingual mucosa; the mucous lining of the cheeks proved to possess the greatest absorptive property. Inflamed mucous membranes exhibit much poorer absorptive power; the reason for this is found in the altered conditions of the tissue, permitting of only scant further intake of fluid. It is also possible, on the other hand, that various single colloids within the mucous cells have undergone certain changes as the result of the inflammatory process, leaving the affected cells with a diminished power of absorption.

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**Oxydase and Similar Reactions in Inflammatory Processes.**

*Georg Herzog, Münch. med. Wchnschr., 69:1300, Sept. 8, 1922.*

With the aid of the oxydase and similar reactions, the author was enabled to demonstrate regularly an abundant development and increase of granulocytes, particularly special granulocytes, in tissues showing inflammatory changes in man, a fact which coincides with the experiences obtained from sections of experimental and human material stained according to the Giemsa technic, and which must be emphasized in contrast with the view of Helly and Sternberg. The cellular proliferation may apparently proceed exceedingly rapidly in inflammatory processes. In accordance with the functional involvement, which depends on the kind and the stage of the actual process, the kind and severity of the etiologic factor, the immunizing-cellular behavior of the latter toward the body and its tissues, etc., various cell forms develop. The investigations undertaken by the author on formalinized frozen sections and on fresh human material include partly suppurative processes, partly inflammatory swellings of lymph-nodes and the spleen

and finally cases of encephalitis and typhoid fever. Winkler's indo-phenol blue reaction with the Schulze A modification, as well as the Loel methods with naphthol-gentian violet and the benzidin reaction were used. In the processes examined, the special granulocytes, which are as a rule characterized in the applied reactions by comparatively larger and particularly dense granulations, were the most prominent. Special consideration should be given to elements with spherolongitudinal, often indented granules, which, in contrast to the special granulocytes, are filled with very delicate, more or less abundant granulations. They probably constitute partially transitional forms of the typical special granulocytes, being observable in the suppurative processes.

Under certain circumstances, very delicately granulated forms are most prominent in certain inflammatory processes, whereas the forms with larger delicate granules are less prominent or absent; the author observed this occurrence in encephalitis and in the typhoid lymph follicles. Without considering all the very delicately granulated cells as absolutely identical, they nevertheless belong in one group in a certain sense and to a certain extent form the connecting link between the lymphoid and phagocytic agranulocytes and the series of neutrophile, eosinophile and basophile granulocytes. In the blood they represent the so-called mononuclears and transitional forms, which may contain the very delicate oxydase granules. The author concludes from his findings, that with the aid of the applied reactions earlier preliminary stages of the ultimate protoplasmic granules can be demonstrated.

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**The Question of Defensive Inflammation.**

*E. Krompecher, Virchow's Arch. f. path. Anat. etc., Berlin, 238: 392, Aug. 14, 1922.*

Aschoff renews the discussion of the question of defensive inflammation. The author believes that both the biologic (teleologic) and the clinicomedical standpoints should be eliminated from the pathologic-anatomic standpoint. From the standpoint of the pathologist, the main reliance must be placed upon a characteristic definition and it can only play the part of, and have the significance of, an explanatory element.

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**Experimental Study of Gastro-Intestinal Movements in Acute Peritonitis.**

*K. Arai, Arch. f. exper. Path. u. Pharmacol., 94: 149, Aug. 11, 1922.*

The author tried different chemical agents and bacteria for producing a uniform and not fatal peritonitis in cats. One-half cubic centimeter of a 2% Lugol's solution per kilogram body weight of cat was injected intraperitoneally and caused a typical serofibrinous peritonitis, which after 2 to 3 days reached its maximum and after 4 to 5 days healed with adhesions. Further experiments with bacteria showed that 0.5 c.c. per kilo of a mixture of staphylococcus and colon



cultures on agar injected into cats intraperitoneally caused a peritonitis in the course of 24-48 hours which healed in 3 days. Larger doses (over 0.7 c.c.) caused death from hemorrhagic peritonitis. Injections of turpentine or of cultures of *Staphylococcus* or *Streptococcus pyogenes* or of colon bacilli did not give definite and uniform results. In all cases of peritonitis produced artificially, a slowing of gastro-intestinal movements was observed roentgenologically, which reached its maximum 24-48 hours after the injection.

The author studied the causes of the disturbance of motility: the iodine as such could not be considered the cause, for potassium iodide stimulates gastro-intestinal movement. On the other hand, cutting the inhibitory intestinal nerves, the splanchnics, in normal cats brought about quicker emptying of the stomach and small intestine. Also the inhibition of gastro-intestinal movements caused by iodine or bacterial peritonitis was overcome by cutting the splanchnics. It could be demonstrated that the intestinal paresis in bacterial peritonitis was favorably influenced by the injection of 10 mg. cholin-hydrochloric acid per kilo.

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(1f—100)

(1f—100)

**Diseases with Labile Dispersion of the Tissue Fluids.**

*R. Geigel, Virchow's Arch. f. path. Anat. etc., Berlin, 238:441, Aug. 14, 1922.*

(1) In bronchial asthma the dispersion of the tissue fluids, decreased during the attack by coagulation and increased by peptization, plays an important part in the production of an attack, as shown by the firm sputum becoming fluid, by Charcot crystals and Curschmann spirals being thrown down, and eosinophilia (coarse granulation) appearing in the polynuclear cells in the sputum and in the blood. Iodine is an effective remedy as it increases the grade of dispersion of the colloids. (2) Eosinophil catarrh behaves quite like bronchial asthma. (3) Pituitary catarrh depends upon the excretion of a thin sputum (of a hydrosol), in which Curschmann's spirals, Charcot crystals and eosinophil cells are also demonstrable. (4) Hay-fever runs a course similar to that of bronchial asthma with associated symptoms of coagulation, eosinophilia and subsequent peptization. The cause of hay-fever is found in pollens of certain gramineae; nevertheless a predisposition or hereditary susceptibility must be present. All of these diseases are characterized by a peculiar hereditary lability of dispersion of the tissue fluids. The attack sets in when the coagulation is predominant and disappears with the onset of peptization.

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(1f—101)

(1f—101)

**The Process of Mummification.**

*S. Goy and E. Wende, Biochem. Ztschr., Berlin, 131:6, July 29, 1922.*

The bodies of 2 new-born infants had lain concealed for a year. Externally the bodies were well preserved, but internally they were almost completely vacuous. Mummification had extended also to the parts that were exposed to the air and therefore subjected to drying.

The sides of the body upon which the corpses had lain showed no difference in composition from the opposite side. Differences were found in the substance of the external skin and the internal muscles. The skin had a higher content of water and of minerals, such as iron; this may be attributed to the fact that the bodies of the infants, which were thrown aside, were probably not washed. The water content was so low that the prolonged preservation of the organic substance is not surprising.

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(1f—102)

(1f—102)

**Examination of Adipocere in Two Bodies.**

*S. Goy and E. Wende, Biochem. Ztschr., Berlin, 131:8, July 29, 1922.*

The body of a man who had been hanged lay for 5 years in a cemetery at quite a high altitude; on the thorax and neck there was adipocere separated by recognizable marks of strangulation. From the mass of adipocere, 98.29% crude fat could be extracted (with ether), 0.26% mineral constituents (0.017% CaO, 0.013% MgO), and 0.04% free glycerin. The reaction was acid. A second corpse, that of a 1 year old child buried 1½ years, was exhumed for examination because of suspected poisoning. No poison could be demonstrated but a grayish-white and a bright pink to red substance was found in the poorly preserved corpse. Tests showed that there was no difference between these two substances. They were composed of 70% crude fat, 5.77-5.93% water, mineral constituents over 3.3%. The fat consisted mostly of a free fatty acid and only a little neutral fat. One-eighth of the total amount had been transformed into calcium, magnesium and ammonium soap.

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(1f—103)

(1f—103)

**A Case of Osteogenesis Imperfecta.**

*Mary F. Lucas Keene, Lancet, London, 203:661, Sept. 23, 1922.*

The fetus was still-born at 8 months. The limbs were very short, the lower extremities were twisted, the vault of the skull was soft, and the pinna not well formed. The shafts of the long bones showed a fibrillated periosteum ruptured in places and containing a pulpy mass consisting of minute islands of osteoid tissue, marrow, and osteoblasts in large numbers. These cells were larger than the normal osteoblast and appeared to be forming a sort of fibrous connective tissue, small masses looking like cartilage, and islands of apparently normal bone. Subperiosteal bone was absent. The marrow was scanty and contained many eosinophils. The thymus was abnormal, weighing only 2.2 gm., and contained a large number of Hassall's corpuscles. Axillary lymph glands showed a paucity of lymphocytes and contained some nucleated red cells and eosinophils. The spleen was relatively large. The immediate cause of the condition seems to be attributable to the osteoblasts, and possibly their impotence was due to lack of calcium salts. There was no evidence of increased absorption of bone. The defect may have been due to the necrotic state of the placenta, but it is interesting to note the association of an atypical thymus with faulty bone production. There was no history of venereal disease in the parents, nor of deformities or malformations in the families of the parents.

(1f—104)

(1f—104)

**Pathology of the Suprarenals.**

*Felix Weissenfeld, Beitr. z. path. Anat. etc., Jena, 70: 516, Aug. 26, 1922.*

(1) In regard to the behavior of the suprarenals in infectious diseases, the author almost always found an edema of the cortex manifested by pushing apart the cell trabeculas. The regularity of edema in the suprarenals in infection is also indicated by the fact that the weight of these suprarenals was not less than normal in spite of their great poverty in lipoids. Poverty in lipoids was always found but it was striking how varying this was in amount in different layers and in different cases. Often the fat was found exclusively in the glomerulosa, in other cases there were remnants in the reticularis, and in still others a disappearance of lipoid in islands in the fasciculata. (2) In a 24 year old puerpera who died after a short illness from influenzal pneumonia with hydrothorax on the right side and deep position of the diaphragm, there was a fresh thrombosis of the suprarenal vein, extension of the thrombus into the vena cava and hemorrhagic infarction of the right suprarenal with good lipoid content. The left suprarenal was macroscopically normal and rich in lipoid. Microscopically the left suprarenal also showed in one place a beginning thrombosis of a central vein and a macular high-grade atrophy of the fasciculata interna. The author saw this latter finding in the suprarenal of another woman who died of puerperal sepsis. It would be interesting to make a further study of these changes in the puerperium. The severe disease of the right suprarenal with a pleural exudate on the right side may have been due to the poor circulatory conditions in the suprarenal on that side. (3) In a case of lipoma of the suprarenal cortex, in the reticularis there was a completely closed accumulation of typical body fat cells with large drops and with a small nucleus pressed against the wall. (4) In the suprarenals of a 53 year old cretin, there were scattered over the whole cortex typical body fat cells which lay clearly in the interstices between the cell trabeculas of the fasciculata and reticularis. In addition to their position and their quite characteristic form, they could be differentiated from the more reddish colored lipoid drops of the cortical cells by their yellower color on Sudan staining.

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(1f—105)

(1f—105)

**Changes in the Suprarenals in Experimental Scurvy with Some Particulars on the Bone Findings.**

*Tomoji Iwabuchi, Beitr. z. path. Anat. etc., Jena, 70: 440, Aug. 26, 1922.*

In the scurvy-like disease produced in guinea-pigs by the feeding of oats, there are always typical changes in the suprarenals: In the cortex there is a pronounced lipoid poverty of the middle part of the zona fasciculata. In the section bounding the zona glomerulosa, the cortical cells are somewhat richer in lipoid. The innermost layer of the fasciculata and the adjacent zona reticularis are richest in lipoid, so that 3 layers of the fasciculata may be distinguished: an external one containing a moderate amount of lipoid, a middle one very poor

in lipoid and an internal one rich in lipoid. The doubly refracting substances almost entirely disappear. They can be found only in traces in the external layer of the fasciculata. In addition to the loss of lipoid, the cells of the middle fasciculata often show degenerative changes in the form of swelling of the cell body and pyknosis of the nucleus. Mitoses are noted with striking frequency. The capillaries, particularly those of the zona reticularis, are filled to turgescence with blood, and considerable hemorrhages are not unusual. The cells of the medulla have almost completely lost their tingibility. The chrome-brown content has disappeared from the vessels. The cells appear small, clear and have a peculiar appearance due to the pyknosis of the nucleus. The vessels of the medulla also are greatly distended with blood. No thrombi or necroses were demonstrated.

The suprarenals of fasting guinea-pigs that were used for purposes of comparison showed the high lipoid content pointed out by most authors. The zona reticularis which is almost free of lipoid in normal guinea-pigs also contains much fat and so the lipoid content seems even greater than normal. The amount of doubly refracting lipoids is decreased as compared with normal. There is no difference in the lipoid content of the suprarenal cortex, whether the animals suffer from an insufficient amount of food over a long period or from sudden total withdrawal of food.

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(1f—106)

(1f—106)

**The Protozoa-Like Formations in the Epithelium of the Uriniferous Tubules in the New-Born.**

*J. Müller, Virchow's Arch. f. path. Anat. etc., Berlin, 238:481, Aug. 14, 1922.*

The author describes 3 cases: (1) The necropsy of a child 8 weeks old showed a chronic internal hydrocephalus, an old and fresh focal nephritis and aspiration pneumonia. In the renal cortex and in isolated parts of the medullary substance there were found lying free in the tubules or grouped around the glomeruli, large cells (up to 30  $\mu$ ) with a protoplasm of foamy structure and a kidney-shaped nucleus which absorbed the pigments of the protoplasm. (2) A still-born fetus 37 cm. long showed no signs of syphilis, but there were subpericardial and subpleural hemorrhages and a congested kidney. There were large cells with a homogeneous nucleus in the membrana propria of the tubules. The protoplasm of the cells was vacuolated. The side of the protoplasm turned toward the lumen showed granules which colored intensively with hemalum. (3) A female child 2 months old showed congenital syphilis, indurative hepatitis with icterus, induration of the spleen and exudative nephritis with focal hemorrhages. In this case also, similar large cells (up to 20  $\mu$ ) were found with enlarged nuclei, recognizable with difficulty, and diffuse granulation (pieces of chromatin) in the region of the necrotic changes in the tubules.

The cells described belong to the organism itself, being cells with homogeneous nuclei derived from the epithelium of the tubules. There is a differentiation between the oxychromatic elements and the basic chromatin, which, having entered the plasma, is found accumulated at the free pole. This degeneration may progress to that state in which only the honeycombed remains of the plasma lie free in the lumina of

the tubules. Therefore these seem to be hyperplastic processes in the renal epithelium leading to the formation of giant cells which then become subject to a peculiar degeneration of the nucleus, associated with regenerative proliferation of the tubular epithelium. Most authorities assume chronic inflammatory irritations (chiefly syphilis) to be the cause of these formations.

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(1f—107)

(1f—107)

**Tissue Malformations in the Neurohypophysis and Infundibulum of Man.**

*A. Priesel, Virchow's Arch. f. path. Anat. etc., Berlin, 238:423, Aug. 14, 1922.*

Altogether the author observed 20 cases, which he classifies into 3 groups: (1) Fifteen cases with small accumulations of cells hardly 1 mm. in diameter, which consist sometimes of epithelial, polygonal cells in stratified or alveolar arrangement, and at other times of spindle-shaped cells united in bundles. (2) Three cases showing nodules about 3 mm. large next to the infundibulum, of a predominant epithelial cellular character. (3) Two cases with hempseed to buckshot sized tumors next to the neurohypophysis, in which the spindle-shaped cellular character is predominant. The following characteristics are common to all these formations: They are either single or numerous (up to 3), white in color, lying in the midline or in its immediate vicinity and standing in a genetic relation to the neuro-epithelium of the primitive infundibulum. They do not produce a disturbance of the organic function of the neurohypophysis. Their histologic structure is fairly uniform. They are strikingly rich in vessels, around which the specific cells of epithelial, or more spindle-like, character are arranged. The character of the cells—their size, granulation and arrangement—suggests that they represent poorly ripened neurogenic elements. This is also suggested by the fact that similar large cells are found in the neurohypophysis. As the spindle-cell type of the glia elements is predominant in the nervous portion of the hypophysis, it is self-evident that such a type should be present in growths resembling tumors, in addition to the epithelial-like cells.

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(1f—108)

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**Observations on the Blood-Vessels of a Meningocele.**

*Ada Stübel, Virchow's Arch. f. path. Anat. etc., Berlin, 238:448, Aug. 14, 1922.*

The author reports his observations with the binocular Zeiss microscope of a Plankton investigation of the blood-vessels of a meningocele, in which the striking fact was noticed that the blood stream became discontinuous and nystagmus-like oscillations appeared on pressure and on crying. After the meningocele was removed surgically and it was put under tension in physiologic sodium chlorid solution of body temperature, the circulation of blood in the arteries and veins was observed even 16 minutes after the operation. The arteries and veins did not empty themselves of blood. By stimulating the surroundings



of the vessels, a very rapid current could be produced. The same reaction occurred when the specimen was moved about. The arterioles were capable of the greatest reaction, whereas the capillaries did not react at all. Similar observations were made on recently operated hernial sacs, hydroceles and on one lymph cyst. The death of the surviving tissue—recognizable by the passage of red blood-cells into the tissues following needle punctures—occurred at the latest after 30 minutes. These experiments depend upon the stimulation of the contractile elements of the vascular wall and the chemical stimulation of the vascular endothelium of the capillaries.

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(1f—109)

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**The Cancer Problem and Studies of Epithelial Growth.**

*Hans Burckhardt, Münch. med. Wchnschr., 69:1365, Sept. 22, 1922.*

There are 2 theories as to the origin of tumors. One holds that tumor is predestined (endogenous theory), the other, that its development depends on external circumstances (exogenous theory). Between these two extremes are grouped all of the tumor theories. In support of the exogenous theory those cases are cited in which it is believed that carcinomas have developed on old inflammations, sarcomas as a result of external violence, etc. But the greatest argument for this theory are the paraffin, Roentgen and anilin cancers. The advocates of the endogenous theory reply that these things are only exciting factors and that they must act upon cells that are already predisposed to cancer. But Fibiger by feeding spiroptera, a species of worm, to rats, produced stomach carcinomas with great frequency, and Yamagiva by painting with tar for many months produced carcinomas of the rabbit's ear; i.e. he succeeded in producing cancer at places where it practically never develops spontaneously. This gives quite a different aspect to paraffin cancer, x-ray cancer, etc. It suggests that the reason why cancer is not always produced is that the action has not been long enough or because it has not been applied in the right way. This does not, however, seem to prove the validity of the extreme exogenous theory. There is a certain parallelism between the strength of normal proliferation in the tissues and the frequency of cancer. This led Ribbert to believe that tumor growth is essentially only a confirmation of the innate capacity for growth of the cells, in so far as it is caused by permanent removal of the physiologic inhibitions to growth. Ribbert has assumed for carcinoma especially that the removal of physiologic tissue resistance is brought about by passive displacement of the epithelial cells in the connective tissue. It may be conceived in conformity with Ribbert's theory that for some reason or other a proliferation of the cells is kept up for a long time and that in the course of many generations of cells the latter acquire a tumor-like character. The comparison of tumor cells to parasites which is often made is justified. In fact, there is no essential difference in the diffusion of cancer cells and of the other parasites, especially bacteria. On the whole the characteristic feature of cancer cells is uninterrupted growth until the death of the individual. The proliferation theory seems to be the most plausible. It leads to the question of whether

it is possible to breed cells, that is, to create conditions in which the cells can follow their innate tendency to growth and in which they can proliferate for any desired length of time. The author used epithelial cells for his experiments on this point. The experiments showed that the epithelium is quite dependent for its existence on the substratum on which it grows. If this is normal (e.g. the cutis), it is permanently preserved, no matter where it is transplanted, of course together with the substratum, provided only that the latter grows. If the substratum is not normal but is ordinary scar-forming connective tissue, the greater part of the epithelium dies as the connective tissue contracts. That there is a limit to cell growth is due to the ordinary contracting, scar-forming connective tissue. The mystic "function of the epithelium to cover surfaces" is reduced in normal epithelium to the fact that it draws its nourishment from normal tissue and grows to such a thickness on the latter as is supported by the nutrition it obtains from the substratum. That epithelium grows only on surfaces is due to the fact that in the deep tissues it is smothered by contracting connective tissue. The author believes that scar-forming tissue plays the part of a protecting policeman in the cell state. Where a group of cells shows a tendency to undergo lawless proliferation and to produce descendents that have a revolutionary character, the connective tissue steps forward and commands them to halt. Where for any reason there is no healthy connective tissue to accomplish this there is an unlimited growth of tissue that in further development may obtain the upper hand over the normal connective tissue.

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(1f—110)

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### **Has Cancer a Pigmentary Origin?**

*Sir George Thomas Beatson, Lancet, London, 203:655, Sept. 23, 1922.*

The author formerly held the opinion that the sex glands might have a powerful connection with carcinoma, if not an actual etiologic relation. Various facts seemed to point that way, but with advancing knowledge of the internal secretions, that line of thought was abandoned. He was first led to think of pigment as a possible factor in the production of cancer when he noticed frequently at autopsies, in cases of some forms of carcinoma, that there was a very pigmented condition of the fat, which evidently contained a coloring matter not present in ordinary fat. A second reason for considering pigment in this connection was that, in the cases of oöphorectomy in which there had been disappearance of the outward manifestations of cancer, the disappearance of the disease was accompanied by an increase in the subcutaneous adipose tissue of the body. This indicated an accession of fat-forming power and also implied an accession of lipoids, which have been considered recently to be of importance both in cellular metabolism and in connection with immunity. A third reason was that an analysis of the fat of cancer patients shows that chemically it differs materially from the fat of normal persons, in that it contains an excess of nonsaturated fatty acids, a difference that points to an abnormal activity of the adipose tissue in cancer patients. A fourth

point has been brought out recently, viz. that there are 2 distinct manifestations of unsaturation activity, one in the vicinity of the growth, the other general, the local being in excess of the general and probably the parent of it. Pigment is a vital force, not only in vegetable life, but also in the animal kingdom, and we are, therefore, justified in regarding it as a possible intrinsic cause of a tissue malady such as cancer. The pigment of the mammary areola may be the active agent by which the secretion of milk is instituted, the pigment working through the mammary chromophores. If this is true, then the pigment must have a close relation to the pathology of breast tumors.

We know of cancer that it is a very ancient disease, that it occurs in all races, that there is an unequal susceptibility to it in various races, and that it exists in all vertebrates. These facts are true also of pigment. In the pigment cell we have a unit which is capable of undergoing the changes that we known must take place in cancer cells. Also, continuous proliferation may be set up in the pigment cell. Experiments have demonstrated that (1) different tumors vary in their power of successful transplantation; (2) the various strains of mice do not show the same susceptibility to successful transplantation; (3) cancer cannot be transferred to animals of another species; (4) there is occasionally spontaneous recovery from transplanted tumors; (5) mice which so recovered could not be successfully reinoculated by transplantation; (6) injection of a tissue similar to the neoplasm caused immunity; and (7) there occurs the gradual development of a carcinoma into a sarcoma. The production of tar cancer in mice has a direct bearing on the subject of this paper.

Of the predisposing causes of cancer, old age, where there are marked changes in the pigment of the body, may be placed first. Cancer is more frequent in females than in males, and under the pigmentary hypothesis, this might be accounted for by the special liability to disease of the breast and uterus, in which pigmentary activity plays an important part. Assuming the correctness of this theory, the sources of pigment in the body must be considered, the chief source being food, which in turn gets the pigment from the soil. Foods grown in manure-fertilized ground may contain deleterious pigments which may be the cause of cancer.

The author admits that he is unable to furnish definite proof in support of his theory, but does feel that the points mentioned are favorable to it.

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#### **Experimental Production of New Growths by Irritation with Coal-Tar.**

*Paszkiewicz, Polska gaz. lek., Cracow, 1:708, Sept. 3, 1922.*

The author made experiments on white rats with reference to the production of new-growths by coal-tar. The irritation was produced by rubbing the tar into the skin of the back every second or third day and by subcutaneous or intracutaneous injection. Unlike Lipschütz, Bierich and Möller, the author could not produce any noteworthy changes. There was neither hyperkeratosis in the epidermis nor proliferation of epithelium; in only a few of the animals was there a

temporary scaliness of the skin. The general condition of the animals remained good. The author believes that irritation of a given part alone does not produce cancer, and that the conditions of life, the kind of food and the nature of the individual and the species play a part in it. Therefore, the results attained in animal experimentation are not comparable with the development of true neoplasms.

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**The Origin and Classification of Epitheliomas of the Salivary and Mucous Glands.**

*E. Krompecher, Beitr. z. path. Anat. etc., Jena, 70:489, Aug. 26, 1922.*

The author describes five cases of tumors of the mucous or salivary glands. In the first case a woman of 35 had had the tumor for 8 years; this proved to be a recurrent mucous cylindroma of the palate the size of a walnut. The second case was one of solid basal cell tumor combined with a mucous cylindroma of the parotid. In the third case, a mucous and hyaline cylindroma involved the antrum of Highmore in a patient of 37. The presence of transition lobules indicates definitely the origin of the 3 aforesaid tumors from the lobule or intermediate part of the mucous and salivary glands. In the fourth case, the partially cornified basal cell or prickle cell cancer apparently was partly due to proliferation of the basal cell layer of the excretory duct, and partly originated from the mucous gland duct of the larynx. In the fifth case, a 50 year old woman had had a tumor for 6 months; this was a pronounced mucous papillary cystadenoma of the lip which originated from the larger excretory ducts of the labial mucous glands. Certain epitheliomas originate from the alveolar epithelium of the mucous and salivary glands, and others from the germinal or basal cell layer of the intermediate portion and from the larger excretory ducts of these glands.

These cases were true intra-acinous or intracanalicular gland tumors. The adenomas and adenocarcinomas originating in the gland tissue and the excretory ducts of the mucous and salivary glands show quite varied histologic pictures. Some of them consist of differentiated epithelium. These include (a) papillary (cylindric cell) cystadenomas or cystadenocarcinomas; (b) mucous cell adenomas or cystadenomacarcinomas, and (c) glandular cell adenomas or adenocarcinomas. Others are composed of undifferentiated epithelium, that is of germinal epithelium or basal epithelium, and correspond to the rarer tumors that have heretofore been described as "mucous cylindromas." For this group the author proposes the name of reticular or mucoreticular basal cell adenomas or basal cell adenocarcinomas. These adenomas or adenocarcinomas of the salivary and mucous glands comprise a comparatively small number of the tumors of the salivary and mucous glands. Like these tumors originating from glandular tissue, the pure pavement epithelial tumors, almost always cancer, are also comparatively rare. The mixed tumors of the mucous and salivary glands, from the histologic findings, are basal cell tumors. The character of the cells, the demonstration of their origin from the germinal

or basal cell layer and their complete conformity with mucous and basal cell tumors of the skin, as well as the similar clinical course strengthen this assumption.

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**A Case of Plexiform Neuroma in the Mesentery of the Small Intestine.**

*Wilhelm Baltisberger, Beitr. z. path. Anat. etc., Jena, 70:459, Aug. 26, 1922.*

The author describes a plexiform neuroma of the mesentery that led to perforation of the small intestine and to a fibropurulent peritonitis. There were also multiple fibromas of the skin and a horseshoe kidney. The plexiform neuroma was almost encircled by a loop of small intestine 48 cm. long, the 2 diameters of which were 15 and 9 cm. respectively. The thickness of the mesentery in the region of the neoplasm was 2.5 cm., while elsewhere it measured 6 mm. The attempt to disentangle the plexiform neuroma failed as the reticular arrangement was very dense. Inside the intestine at the place in the wall corresponding to the broadened insertion of the mesentery, there were numerous sickle-shaped folds which projected as much as 8 mm. into the lumen. They were distant 0.5-1.5 cm. from one another, but had nothing to do with Kerkring's folds; were 6-8 mm. broad, firm in consistency, could not be made to disappear by traction in the longitudinal direction, and their circular extent was limited to the insertion of the mesentery. These folds arose almost perpendicularly from the intestinal wall and fell away again as suddenly on the other side, to rise again after a short interval. A section through this structure showed that they were due to a thickening of the layers lying inside the musculature, the submucosa and the mucosa. That section which apparently corresponded to the latter had a uniformly homogeneous white appearance; but the zone which represented the submucosa showed a certain degree of structure.

As to the structure of the tissue enclosing the neoplasm, the histologic structure of the cords in general and the condition of the nerve fibers, there were no variations from the findings described in the literature. In the examination of different specimens, it was found that the perineurium and endoneurium were not uniformly involved in the proliferation. Often there was only connective tissue of the endoneural type, and the perineurium surrounded the nodule as a concentric mantle merely. In several cases ganglion cells were found in nodules. They always lay in the midst of proliferated connective tissue. The nerves irradiating into the intestinal wall showed numerous nodular thickenings which sometimes followed one another so closely that they flattened each other. The submucous plexus showed great changes which were partly the reason for the above-described macroscopically visible sickle-shaped folds inside the intestine. It was a diffuse hyperplasia of the mucosa and submucosa of the intestinal wall at various places which was limited chiefly to the nervous constituents. Meissner's plexus at these places seemed to be enormously enlarged and provided with numerous ganglion cells. Moreover it was affected by a diffuse fibromatosis which did not stop at the muscularis mucosae but



extended through this to the nerve fibers supplying all the glands and villi. The author speaks of it as a sort of elephantiasis.

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**The Morphology and Development of Papilloma Coralli-forma.**

*Friedrich Schmidt, Virchow's Arch. f. path. Anat. etc., Berlin, 238:453, Aug. 14, 1922.*

This observation includes 2 cases of localized papillomas of the esophagus in cattle. About 41 little tumors were excised with their surroundings and examined histologically. In the first case, for a distance of 32 cm., and in the second case for 20.5 cm., the surface was covered with a number of single little tumors, varying from hardly perceptible nodules to papillary trees 5 cm. high. In the first case vegetable hairs supplied with fine serrations were found in the papillomatous mucous membrane. Seven types of proliferations were differentiated: (1) A strikingly marked corrugation appears at the summit of the folds of the mucosa in a circumscribed area, indicating the beginning of a papillomatous proliferation. (2) The simplest forms of unbranched, enlarged single papillas appear on the mucosa adjacent to branched papillomas. (3) More or less numerous branches are grouped together in a bunch on a common, separate pedicle. The most numerous and the largest papillomas belong to this group. (4) This type resembles Type 3 in being formed like a cabbage head or a cauliflower but is without a pedicle. (5) A large plaquelike tumor is situated on a short pedicle, due to cessation of the longitudinal growth of the connective-tissue main stem, whereas the ramifications grow centrifugally to an extraordinary degree (observed once). (6) These are unbranched papillomas, the surfaces of which appear like a grater as a result of countless numbers of the most delicate serrations. (7) The papillomas show a leaf-shaped form, resulting from growth in all 3 directions.

The histologic examination shows a connective-tissue plug reaching to the extreme end of the papilloma, carrying numerous vessels and forming the main stem of every growth. This connective-tissue main stem is covered by a stratified layer of pavement epithelium (with all 3 strata of the skin). Even in the outermost layer (stratum corneum) the cells still have nuclei. Many papillas take part in the growth of every papilloma. Simple hyperplasia of the preformed papillas is rare. The author believes that the traumatic irritation from hard grains of corn is inadequate to explain the cause of these formations and that an infectious or chemical noxa must be present in addition.

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(1f—115)

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**Congenital Hypertrophy of the Heart Caused by Diffuse Rhabdomyoma.**

*Alexander Schmincke, Beitr. z. path. Anat. etc., Jena, 70:513, Aug. 26, 1922.*

This was the heart of a strong male child who from his size and weight was apparently full term and who showed the signs of

maturity, but who died immediately after delivery. The heart was double the size of a fist and weighed 46 gm. but aside from its abnormal size was typical in form. The walls of all the cavities were very much thickened, especially that of the right auricle. In the microscopic examination the following points were noteworthy: The thickened walls, on cross-section, showed round and irregularly shaped fields at the periphery of which were fine fibrillary longitudinal and transverse striations, while the central part was either nonnucleated or contained round nuclei. Among the fields there were small vessels at different places. The impression that these fields were cross-sections of embryonic heart muscle fibers was confirmed by the characteristic picture of the fibers where they were cut longitudinally in the specimen. Here was seen the picture of sarcoplasm cylinders with a fibrillary differentiated mantel zone which is characteristic of embryonic fibers.

The aforesaid findings could be demonstrated uniformly in all the thickened parts of the heart wall; in the region of the papillary muscles, where the wall was only slightly thickened, there were also differentiated fibers with fibrillary sarcoplasm on all sides. This was a case of diffuse rhabdomyoma of the heart characterized by the fact that the whole organ was involved in the tumor-forming process and to a certain extent the heart itself represented the tumor.

# International Medical and Surgical Survey

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BACTERIOLOGY

1a. ANATOMY AND PHYSIOLOGY

ANATOMY, EMBRYOLOGY, HISTOLOGY

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**Darwinism and Lamarckism. The Cross-Section Quotient of the Muscles.**

*Hermann Triepel, Anat. Anz., Jena, 56:181, Nov. 1, 1922.*

Darwin assumed that there was an inheritance of so-called characteristics and explained this with the aid of the germinal theory. From this point of view there is identity with Lamarckism. Triepel stands equally for the selection and the adaptation theory. Lamarckism tries to explain the development of a characteristic, a quality, while Darwinism explains its preservation in the greatest possible perfection. Selection can only choose from what is present; it cannot create anything new. The sympathetic coloring of an animal, which blends into that of his surroundings, is a protective coloring, and gives the protected individual an advantage over his companions who are not so colored or are insufficiently colored, and it can, therefore, be strengthened by natural selection. The nature of its origin is of no consequence in the effectiveness of the principle of selection. The conditions are similar in the imitation of the form of markings—mimicry. In this connection attention is called to the brushes on the inner side of the tarsus of the hind legs of worker bees. As they are excluded from propagation it is questionable whether these brushes which are so useful for the whole bee community can be preserved or improved by selection. The race with well developed brushes is superior to others and easily preserves these brushes by inheritance. The secondary, or, more properly speaking, accessory sexual characteristics of many males—production of special tones and ornamental characteristics such as beautiful colors—serve in the struggle for the females for their sensual excitement, not, as Darwin says, to make the females select them. Sexual selection is a natural one.

The causes for the origin of the characteristics for selection lie, according to Darwin, in independent changes of the germ plasm, in independent variations of the anlage. This is impossible; of itself nothing can change its condition; there are generally 2 factors necessary for that. Lamarckism is based on the consequences of use and disuse, and only after that one considers the action of external factors which cause a reaction or function of one or more parts of the organism. For example, according to Schiefferdecker the hairlessness of man is to be attributed to the fact that hair became superfluous because of the high development of other heat-regulating mechanisms—the central nervous system. The greatest economy of development and the resulting automatic regulation of organ formation are thus harmoniously adjusted; this touches on the principle of partial selection

introduced by Roux. At any rate the present living organic world is due to the interaction of 2 different kinds of happenings, the causally determined life of the organism itself and the action of the external factors upon it.

According to Lamarckism we must reckon with the use and nonuse of organs as well as with the direct action of external factors and recognition must be accorded not only to the natural and sexual selection of Darwin but also to the partial selection of Roux and the principle of the greatest economy during development. The latter is identical with the principle of the smallest action. When an external factor influences not only the phenotype but also influences the genotype immediately, it is easy to understand the inheritance of the acquired change, as the question of the means by which the newly acquired characteristic is transmitted is superfluous. The study of the muscle was based on the consideration that the proportion between the muscle cross-section ( $Q_m$ ) and the tendon cross-section ( $Q_s$ ), which is called the cross-section quotient ( $Q_q$ ), must not go beyond a certain measure, that is determined by the value of the muscle strength  $F$  and the tensile strength of the tendon  $K_z$ .  $Q_m$  can be considerably increased by exercise, which must be followed in functional adaptation by an increase in  $Q_s$ , in order not to bring about rupture of the tendon. But  $Q_s$  remains somewhat less and the quotient increases, that is, the cross-section of the tendon does not fully keep pace with that of the muscle. The tendon cross-section is much more constant during the life of the individual than the muscle cross-section. The quotient differs with different muscles; the semitendinosus showed the largest, and the extensor carpi radialis prim. the smallest, quotient and the gracilis stood between them.

If we understand by activity of use the frequency of this use and the strength of innervation as well as the size of the resistance to be overcome, the different muscles must differ in activity during the individual life. Muscles with small quotients, that is, comparatively large tendon cross-sections, must have acquired the thickness of the tendon not only by functional adaptation, but there must have been an increase in thickness independent of function. This is due to inheritance, as the ancestors of the individual made unequally active use of the muscle in question. In comparing apes (*Cynomolgus sinicus*) with men it was found that the cross-sections of muscles with the exception of the extensor carpi radialis prim. were larger in the right arm than in the left, and the quotients were correspondingly larger. Conversely, they were larger in the left leg, the quotients were larger in every second muscle than on the right and vice versa. In anthropoids (orang) the right arm and the left leg are longer; in the lower apes the conditions vary.

In *Cynomolgus* as in man, the quotients of the hind extremities are greater than those of the front ones. The muscles of the latter are stationary or regressive in *Cynomolgus*, while the muscles of the hind legs are progressive with the exception of the plantaris, which, like the biceps humeri in man, is especially well developed. If the thickness of the tendon is partly acquired during autogenesis by function and partly inherited and acquired through phylogenesis, this shows the inheritance of a functionally acquired change of the phenotype. The tendon of a muscle must be thickened by activity, and during autogenesis as well

as phylogenesis the cross-section of the tendon is more stable than that of the muscle. If a large cross-section quotient indicates a progressive, a small one a stationary, and a very small one a regressive, stage of phylogenetic development of the muscle, this must be brought into causal relation with the activity of its present use.

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**Radiology in the Teaching of Anatomy.**

*J. M. Woodburn Morison, Brit. M. J., London, p. 795, Oct. 28, 1922.*

While anatomists for many years have used radiographs to illustrate lectures and demonstrations, the staff of Manchester University now includes a radiologist (the author) who works with the professor of anatomy, giving demonstrations related to the general scheme of teaching. After reviewing the discovery of x-rays by Roentgen in 1895, the students are shown how x-rays penetrate objects in direct proportion to their density. Different densities of human tissues are considered, and also the action of x-rays on the fluorescent screen and photographic plates. The student then understands he is dealing with a series of superimposed shadows, requiring interpretation. Next follows the x-ray study of a long bone, and how the series of superimposed shadows is produced. Subsequently, normal and abnormal bones are studied (emphasizing the necessity of knowledge of the normal), then the chest, the alimentary tract and the urinary tract, the students screening each other, and thus acquiring proper technic. This is easily acquired with apparatus and methods standardized, but interpretation of the radiographs is difficult; for this a knowledge of anatomy is essential. The research student finds radiography useful in many ways, such as investigating the blood supply of different organs. In conclusion, Morison claims that radiology is of use in the teaching of anatomy, inasmuch as it gives the student some idea of the structure of the living body, which he can compare with work in the dissecting room. He becomes aware that his anatomic knowledge will be of use in his everyday work as an intelligent practitioner of medicine. Radiology makes a knowledge of living anatomy possible, and its use in the teaching of anatomy brings the anatomist and radiologist into a communion which is mutually helpful.

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**The Structure of the Vertebrate Head.**

*W. B. Primrose, Brit. M. J., London, p. 796, Oct. 28, 1922.*

It is shown that the structure of the vertebrate head is based upon the first metameric segment of the body, with which is combined an unsegmented structure called the face. The principle followed is that structures arising in the same morphologic position, at the same period of evolution, and in the same manner, are homologous structures, and form a morphologic unit. When a structure is formed it acquires 2 distinct relations: (1) The relation it bears to the structure responsible for its formation; this is constant and may be called the morphologic relation. (2) The relation it bears to any and every other structure;

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such relations are secondary (anatomic) and are variable to an endless degree. Applying this principle of identity of origin and of relation to the skeleton of the head, it is found that this skeleton consists of 4 morphologically distinct skeletons not separable anatomically. In order of appearance they are: (1) the sclerotome skeleton; (2) axial skeleton; (3) splanchnic skeleton; and (4) facial skeleton. The difference of the 4 skeletons in the head is outlined. The myotome and mesoderm are discussed; the mesoderm gives rise to all the muscles of the head; none is formed from myotomes, which conclusion is in agreement both with evolutionary history and embryologic investigation. After discussion of the splanchnopleure of the head segment, this theory is presented: a simple, almost unmodified, metameric segment is the morphologic basis of the vertebrate head, and the mesodermic segment has given place to structures more suitable and efficient for the changed conditions. Little remains now of the primitive segment. The one structure pointing to the segmented condition is the internal carotid artery, which, through all the evolution of segmented chordate animals, has maintained its segmental independence as the spinal artery of the head segment.

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**The Cranial Anatomy of Polypterus, with Special Reference to Polypterus Bichir.**

*Edward Phelps Allis, Jr., J. Anat., London, 56: 189, April, July, 1922.*

The author's work was begun in 1899 on 2 large specimens of *Polypterus bichir*, later supplemented by 3 heads of *Polypterus ornatipinnis*, 4 specimens of *Polypterus Lapradei* (said to be *Polypterus bichir*) and three larvae of *Polypterus sengalus*. The author found that the cranium of *Polypterus* is platybasic, and several of the cranial bones correspond, in topographic position and relations, to two or more of the bones of recent *Holostei* and *Teleostei*. These several bones are the basiexoccipital, the parietodermopterotic, the postfrontosphenotic, the premaxillary, the maxillary, the cheek-plate, and the sphenoid. The nasal, accessory nasal and os terminale are wholly separate in this fish. There is a large opisthotic, which is partly of primary and partly of secondary origin. The dental arcade is apparently similar to that of *Mammalia*. The trigeminofacialis chamber consists of a trigeminus chamber and a jugular canal, the latter canal apparently representing a primitive condition of the facialis part of the entire chamber. The common carotid artery traverses the canalis parabasalis through the ascending process of the parasphenoid and enters the ventral portion of the trigeminus chamber, where it gives off an ophthalmic branch, which accompanies the ramus ophthalmicus superficialis trigemini. The jugular vein is formed by the union of supra-orbital and infra-orbital veins. The nervus terminalis is apparently represented by 2 nervus strands that arise from the bulbus olfactorius and accompany the nervus olfactorius into the nasal sac. The eye muscles are innervated as they are in the *Ganoidei* and *Siluridae*, excepting that the inferior division of the nervus oculomotorius passes dorsal, instead of ventral, to the musculus rectus inferior. The radix profundus, which apparently contains only general sensory fibers, issues

from the cranial cavity with the nervus oculomotorius, and a ganglion then immediately forms upon it. The nervus trigeminus contains motor, general sensory, communis and lateralis fibers, the communis and lateralis fibers arising from the medulla with the corresponding roots of the nervus facialis. The radix facialis apparently contains only motor, lateralis and communis fibers. The radix issues from the cranial cavity into the jugular canal, and a ganglion forms on it which is partly intracranial and partly extracranial in position. The nervus glossopharyngeus contains motor, communis and lateralis fibers, but apparently no general sensory ones. The nervus vagus contains motor, general sensory, communis and lateralis fibers, the latter fibers all entering the ramus supratemporalis vagi and the nervus lineae lateralis.

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### **The Hypophysis of a Chimpanzee.**

*Alfred Plaut, Anat. Anz., Jena, 56:177, Nov. 1, 1922.*

The hypophysis, secured at autopsy from a female chimpanzee 11 years old (the pars tuberalis remaining in the skull), was relatively large (10 by 7 by 5 mm.), as the female was a virgin. It was microscopically and macroscopically much like that of man, especially the pars intermedia. In the higher mammals this is a very characteristic structure with marked separation between the anterior and posterior lobes. This division cannot be found in man; in place of the pars intermedia there are cysts and fissures filled with colloid, and for long stretches the aforesaid lobes come into immediate contact. The region of the pars intermedia in the chimpanzee contained a colloid mass, probably belonging to the anterior lobe, and anteriorly it was bounded by the cell trabeculae of the anterior lobe, and posteriorly was cut off from the rest of the hypophysis cavity by a compact strip of connective tissue. At the border of this a piece of the cyst projected into the posterior lobe. The epithelium was preserved and resembled throughout the low to cubical, slightly basophil, nongranular or finely granular pars intermedia cells; in a small area the cells were pressed close together; the deeply stained nuclei lay quite at the base; the cell body was high cylindrical and with hematoxylin-Delafield eosin stained a pale mauve color with sharp cell boundaries. As this part of the colloid filled space certainly belonged to the pars intermedia, it was assumed that there was a coalescence with the neighboring hollow space formed by the liquefaction of anterior lobe tissue. At the other pole of the hypophysis cavity colloid masses reached into the pars nervosa, and there were no pars intermedia cells. The remnant of the cavity was surrounded by compact connective tissue poor in nuclei, containing many elastic fibers. It looked like a small fissure occupying about one-tenth of the lobe boundary and lined with 2 layers of epithelium. On the anterior wall the nuclei were smaller and contained more chromatin than on the posterior. In a very small part of the posterior wall pars intermedia cells lay beside one another, as in other mammals. From the posterior wall of the remnant of the cavity some acini, consisting of pars intermedia cells, projected into the posterior lobe, which in a few places were divided from the posterior lobe tissue by a propria. No epithelial cells penetrated into the pars nervosa; colloid



was contained in the pieces of tissue. The hypophysis cavity remnant was small and distinguished from the neighboring spaces particularly by its wall of strong connective tissue containing many elastic fibers, the neighboring spaces being bounded only by thin stroma or immediately by the cell trabeculae of the anterior lobe. This gave a means of distinguishing between primary cysts (rests of the embryonic cavity) and secondary cysts developing in postnatal life. The large colloid mass lying at the boundary of the lobe had the same staining reaction (polychrome on methylene-blue and tannic acid fuchsin) as the colloid mass of the anterior lobe. The large amounts anteriorly were an unusual finding, at least in the human hypophysis. The boundary consisted in part of degenerating eosinophil cells, partly of cells rich in protoplasm with a finely granular plasm that was neither strongly basophil nor strongly eosinophil. The findings were similar in the anterior lobe of the hypophysis of the dog. There was also colloid in the veins of the anterior lobe. Only a few epithelial elements penetrated the glious lobes; pigment could not be found.

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**Anatomic Notes on the Accessory Organs of the Eye of the Horse.**

*Sir Frederick Smith, J. Anat., London, 56: 366, April, July, 1922.*

The orbit of the horse is not a bony cavity. The periorbita forms a membranous socket for the eyeball, and especially for its accessory organs. The periorbita is a cone-shaped fibro-elastic bag extending from the optic hiatus of the sphenoid bone to the margin of the orbit; it originates from the dura mater surrounding the structures which enter the orbital hiatus through the various foramina. All the muscles of the eyeball, including those of the eyelid, arise within the periorbita. The fascia of the globe is complex in its arrangement. Roughly speaking, there are 2 layers of fascia, an outer and an inner, both of which are derived from the recti muscles. Quite distinct from the fascial sheaths of the recti muscles is Tenon's capsule, a thin, diaphanous membrane found within the orbital sheath. It extends from the optic hiatus to the eyeball and is reflected inward in such a way that every muscle receives a sheath of it. The nerves to the eyeball muscles are supplied by the third, fourth, fifth and sixth cranial nerves. Two distinct branches of the fifth, the ophthalmic and superior maxillary divisions, are engaged. The nerve supply is sensory, motor and secretory; both branches of the fifth are sensory, the third, fourth and sixth are motor. The secretory nerves are contained in the fifth and sympathetic.

Fat is abundant, both in deposits and layers, between and outside the eyeball muscles and within and outside the periorbita.

The third eyelid is placed at the inner canthus of the eye; it consists of a deep-seated and a visible portion. The latter can be seen from the front attached both above and below to the conjunctiva. On both temporal and nasal surfaces of the visible portion a cavity can be made by introducing the forefinger, which will enter as far as the first joint; both surfaces are covered by conjunctiva. The lacrimal gland is a spleen-shaped body about 65 mm. in length and 35 mm. in width. It fills up the entire space between the orbital process and the eyeball.

Its extremely small excretory ducts open into the conjunctival sac by minute openings at the outer canthus. The lacrimal puncta in the lids are situated about 2 or 3 mm. above and below the caruncula and lead into the lacrimal ducts. The remarkable feature about both ducts and sac is their relatively large size; the ducts are several times larger in diameter than the puncta. The lacrimal sac is concave posteriorly and the duct leading from it to the nasal chamber has a remarkably thick corrugated inner wall. The basis of each eyelid is a layer of periorbita which in the upper lid enters directly. The structures found in the lids, detailed from within outwards, are: conjunctiva, levator muscle, periorbita, fascia, orbicularis muscle and skin. Each lid contains well-marked tarsal cartilage and meibomian glands.

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**A. New Interpretation of the Bones in the Palate and Upper Jaw of Fishes. I.**

*H. Leighton Kesteven, J. Anat., London, 56:307, April, July, 1922.*

For this work the author has chosen as a typical teleostean palate that of *Promicrops*, a member of the *Serranidae*, and in no way unique. The description of the upper jaw and palate was carefully checked by the study of each bone separately, and by rearticulation of the components. He has found that the premaxilla articulates with 1 bone only, the maxilla of its own side. Each is a tapering, slightly curved rod, presenting on the ventromesial aspect of the curve an attenuated isosceles triangular area closely set with strong, sharp conical teeth. In the midline the bones unite one with the other by a fibrocartilaginous union, and on either side of this symphysis send upward a pyramidal process, which latter, in other forms, has been designated the ascending process of the premaxilla. The maxilla is composed of a head, a shaft and a distal spatulate portion. The swollen head of the bone lies for the most part behind the base and lateral process of the ascending process of the premaxilla, being extensively hollowed out to articulate therewith. The vomer presents an enlarged body and a tapering, laminate posterior process. The upper portion of the anterior surface of the body of the vomer together with the anterior surfaces of the mesethmoid and parethmoids constitute the sloping posterior bony wall of the nasal organs. Anteriorly, the parasphenoid becomes laterally compressed and extends far forward above the posterior process of the vomer to articulate not only with the posterior aspect of the ascending portion of the body of that bone, but also with the mesethmoid and the inner edges of the parethmoids. The palatine bone articulates with the parethmoid in 2 places, and bears 2 facets for these articulations. As viewed from the palatine aspect, the bone is triangular in outline. The pterygoid is a roughly boomerang-shaped bone, but with a short, broad spur standing out in a posteromesial direction from near the center of the convex edge. Behind the palatine the outer border is free. The inner edge articulates with the mesopterygoid as far back as the tip of the spur, and behind this with the quadrate. The blunt tip of the spur reaches the metapterygoid. The mesethmoid, situated immediately above the ascending face of the vomer, suturates with the parethmoid on each

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side, and also forms a squamous suture with the anteromesial edges of the frontals, the latter bone being the superficial element in the suture. (Most of these structures are well illustrated in the figures which accompany the article.)

The structures enumerated are given the following new interpretations by the author: (1) the maxilla and premaxillae of the majority of teleostan fish constitute an adventitious jaw, and are not homologous with the similarly named bones in other vertebrates; (2) the labial cartilages, well developed in most Elasmobranchs, present in 1 teleostome, and evanescent in amphibia, are structures homologous with the teleostean maxilla and premaxilla; (3) the vomer of teleosts is homologous with the premaxillae of other vertebrates; it is certainly not the vomer of other vertebrates; (4) the anterior portion of the parasphenoid of the teleosts is the homologue of the vomer of other vertebrates; (5) the palatine of the teleostan skull is the homologue of the maxilla of other vertebrates; (6) the mesopterygoid is the palatine; (7) the pterygoid is the quadratojugal or jugal; (8) the quadrate has been correctly homologized; (9) the metapterygoid is the amphibian pterygoid; (10) the parasphenoid corresponds to the vomer and pterygoids of the reptile; and (11) the parethmoid is the homologue of the reptilian prefrontal.

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**Some Observations on the Shape of the Palate in Children.**

*W. Kerr Connell, Brit. M. J., London, p. 800, Oct. 28, 1922.*

These remarks are based on a study of over 1000 dental impressions (bites) obtained from the mouths of school children 4-14 years of age. The bites were obtained in the following way: A layer of plasticin (2 mm. thick) was spread evenly on oblong cards, and the children were asked to bite on these cards, leaving impressions of their teeth. Age and sex were noted. Each bite was placed beneath thin square-millimeter paper, previously rendered completely transparent by moistening with cedar-wood oil. Thus accurate tracings of the bites were made, so they could be easily and correctly measured. The reasons for collecting a series of bites were (1) to learn something about the chief variations in the shape of the palate; also the relative incidence of these shapes at different ages in both sexes; (2) to see what variations, if any, may be caused by certain diseases (adenoids); (3) to gain information about the growth of the palate; (4) to obtain statistics regarding periods of eruption of certain of the permanent teeth; and (5) to learn whether the size of the palate bears any relation to the general size and development of the individual. Findings: (1) Nine distinct types were found; most frequent were oval, 57.18%; wide oval, 11.59%; pointed, 7.81%; narrow oval, 6.55%; square, 4.29%. Narrow ovals were commoner in girls; squares commoner in boys. (2) In bites from patients with pronounced adenoids, little or no deviation from normal was seen. (3) Further statistics are necessary but there was a slight fall in intercanine measurement between 11-14 years, indicating an actual absorption of bone in this situation. (4) Eruption occurs earlier in males but is more rapidly completed in females. (5) Size of the palate bears absolutely no relation to the general size and development of the individual child.

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**The Anatomy of the Bone-Marrow, with Special Reference to the Distribution of the Red Marrow.**

*A. Piney, Brit. M. J., London, p. 792, Oct. 28, 1922.*

Absence of information on the normal anatomy of the bone-marrow is the justification for this paper. The red bone-marrow is the principal hematopoietic tissue in the adult, and is not only a simple material serving to render the bones solid without unduly increasing their weight, but is the factory in which all the formed elements of the blood are produced, with perhaps the exception of the lymphocytes. Disorders of the red bone-marrow are associated with irregularities in the production of antisubstances, and apparently it is the principal arsenal of the defensive forces of the body. Selection of material for the study of the normal distribution of the red bone-marrow requires care; only material from cases of sudden death in previously healthy persons can be employed. Pictures of the marrow changes throughout life show a progressive diminution in the relative amount of cellular marrow in the limb bones and progressive increase in the amount of fat. Examination of a series of adult marrows leads one to imagine that there had been centripetal spread of the fat, thus leading to the filling of the more distal parts of the long bones with fat. Examination of the limb bones of a subject 16-18 years old might lead to the belief that the red marrow was mainly confined to the ends of the long bones. The adult condition of distribution is reached about the twenty-fifth year, but some of the bones reach their final distribution at an earlier age. Arrangement of the blood-vessels in the red marrow is the essential factor in hematopoiesis, the 2 main types of cells—red and white—being produced in relation to different parts of the vascular system of the marrow.

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**On the Hypotrochanteric Fossa and Accessory Abductor Groove of the Primate Femur.**

*A. B. Appleton, J. Anat., London, 56:295, April, July, 1922.*

In 1883 Houzé called attention to the occasional replacement in man of the gluteal ridge by a fossa which he named the "fossa hypotrochanterica." Appleton points out the presence of certain fossas in a similar position in other primate femora, which cannot be identified with the fossa hypotrochanterica of man, since they are of a totally different nature. The author urges caution in the employment of the "fossa hypotrochanterica" for the natural classification of primates. The name "fossa hypotrochanterica" is conveniently reserved for a fossa, groove or pit at the site of insertion of the gluteus maximus on the femur. In addition to this depression there occurs another groove on the posterior aspect of the primate femur, in the neighborhood of the lesser trochanter. It provides attachment for a specialized portion of the adductor musculature, and is given the name of "accessory adductor groove." With the specialization of 2 accessory adductor aponeuroses in certain Catarrhinae, 2 corresponding grooves make their appearance on the femur. Grooves are also present in many primates at the sites of attachment of the pectineus, adductores longus and brevis.

All these fossas and grooves may be replaced by ridges, the frequency of which varies in different species. With the reduction of the accessory adductor musculature in man, there is an absence of any special groove or ridge for its attachment. In man the hypotrochanteric fossa occupies a position approximating to that of the accessory groove in other primates. Three excellent figures illustrate the location of the anatomic structures discussed.

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**The Structure and Origin of the Lymph Sinuses of Mammalian Lymph-Nodes and Their Relations to Endothelium and Reticulum.**

*Hal Downey, Haematologica, 3:431, Sept., 1922.*

As the result of comprehensive studies on experimental and pathologic material, the author is of the opinion that the lymph-sinuses of adult mammalian lymph-nodes are channels in the reticulum which are not lined with endothelium. The precise nature of the cells lining the lymph-sinuses of lymph-nodes, venous sinuses of the spleen and bone-marrow and the sinusoids of the liver, and their relation to the endothelial cells of the blood-vessels have been subjects for much discussion. According to Aschoff, the cells lining these sinuses are functionally equivalent to the clasmatocytes of the loose connective tissue and omentum. The sinuses are so closely associated with the reticular tissue of the organs concerned that a careful study of this reticulum with the aid of the best modern methods for bringing out the fibers as well as the cells is necessary. Downey carried out his studies on the mesenteric lymph-nodes of adult cats and rabbits, on pig embryos and on a pathologic human lymph-node (lymphoma, aleukemia ? ). In order to demonstrate clearly the relations between the reticular fibers and their cells, a combination of Mallory's phosphomolybdic hematoxylin, Krause's iodopotassic iodid gold chlorid and the May-Giemsa blood stain proved most satisfactory.

It was found that the tissue bordering the lymph-sinuses was continuous with the general reticulum of the nodes. It was both fibrous and cellular, the fibers being embedded in the cytoplasm of the cells and occupying the same position as they do in the reticulum cells of other regions of the nodes. The study of developing mesenteric nodes of pig embryos showed that these lymph-channels originate as lacunas in the mesenchyma, and that their connection with the neighboring plexus of lymph-vessels is secondary. The endothelium of the lymph-vessels fails to grow into these channels. These primitive lacunas increase in number and complexity and the surrounding mesenchyma differentiates into the reticulum of the adult nodes. The lacunas remain as unlined channels through the reticulum. The reticulum of the sinuses shows the same phagocytic activity and ability to give off free cells that is characteristic for the reticulum of other regions of the nodes. In structure and physiology it is very different from the endothelium of blood-vessels and lymph-vessels. The venous sinuses of the spleen are also composed of reticulum which in pig embryos is derived from the local mesenchyma. According to the embryologic researches of Mollier and Neumann, the



blood sinuses of the liver are also lined by reticulum rather than endothelium. Further morphologic investigations are necessary before it can be definitely stated whether this is true for the sinuses of the bone-marrow, suprarenal body, and possibly also of the thyroid and kidneys.

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### What are Viscera?

*C. Judson Herrick, J. Anat., London, 56:167, April, July, 1922.*

The traditional term viscera has been so loosely applied to various types of anatomic structures that the use of the word is often ambiguous and confusing. Herrick believes that, if one considers the matter from the physiologic standpoint, it is possible to frame a definition which, though not free from objections and confusing exceptions, is nevertheless generally serviceable. In a functional analysis of the animal body 3 classes of organs must be recognized: (1) visceral, (2) somatic, and (3) ambiguous or transmutant, in origin belonging to one of the two primary types but secondarily transformed wholly or in part into the other. The third class cannot be eliminated or ignored, for organisms are not static but are ever in flux, and old materials may be transformed and put to new uses quite at variance with any formal rules which may be laid down in logical systems.

Sherrington has divided the receptive organs into exteroceptors, interoceptors and proprioceptors. The related afferent nerves and their central connections readily fall into the corresponding classes, and if to each of these systems one joins the neuromotor mechanisms most directly related, the way is opened up for a fundamental analysis of all the organs of the body. The exteroceptors and related neuromotor apparatus are primarily concerned with the adjustment of the body or its members to external conditions. Since this usually involves a change in the relations of the body as a whole to its environment, these systems in the aggregate may be called somatic. The interoceptors and related neuromuscular apparatus, on the other hand, are primarily concerned with internal adjustments of the body, its conservation and reproduction. The mechanisms here employed are, in the main, those classed as viscera in the dissecting room, and, accordingly, these are called the visceral or splanchnic systems. The proprioceptors ensure the coördinated or synergic action of the motor apparatus. They are internally excited, but not necessarily visceral. By far the larger part of the proprioceptive system is ancillary to the skeletal musculature and is, therefore, somatic in type as the author has defined this term. Any proprioceptors which are excited by the action of visceral muscles would also have to be classed with the visceral systems.

Concerning the numerous cases in which undoubtedly visceral organs of primitive species have, in the course of evolution, assumed somatic functions and conversely, the author says that in the case of primitively visceral structures which have secondarily acquired somatic functions one must choose whether to classify them as visceral along with their homologues in lower forms in accordance with their genetic relationships, or as somatic, recognizing only their status in the definitive stage.

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**The Misuse of the Term "Visceral."**

*Raymond A. Dart, J. Anat., London, 56:177, April, July, 1922.*

The object of this communication is to trace briefly the history of the confusion in modern neurologic and physiologic literature arising out of an unrestrained use of the term visceral. The word was originally used in the sense of "pertaining to viscus," as opposed to "parietal." The term was also applied to the unstriated, endodermal musculature of the gut or other viscera in contradistinction to the so-called dermal (ectodermal) musculature. In osteology the use of the term visceral became fairly well established because it afforded a convenient distinction between the cranial skeletal elements developed in apparent adaptation to the digestive tube and its requirements (viscerocranium) and those evolved in adaptation to the sense organs and the neural tube (neurocranium). Concerning the use of the term visceral in the muscular system, the author calls attention to Schneider's (1879) attempt at a comparative myology of Chordata. Schneider divided the musculature of Chordata into the smooth and striated varieties quite correctly, but he subdivided the striated musculature into 2 subsidiary groupings, viz., body or parietal musculature and visceral musculature, a classification lacking even in internal harmony and morphologically worthless, according to Dart.

In neurology the author is of the opinion that the term visceral (afferent or efferent) can have no morphologic significance apart from its limitation to the vegetative innervation of the endodermal lining of the archenteric tube and its derivatives. As such it may include presumably afferent elements, by means of which the viscera are brought into more or less intimate connection with the central nervous system. But as soon as the visceral (endodermal) elements become entangled in description with the ectodermal portion of the vegetative nervous system, in supposed contradistinction to the so-called somatic nervous system, confusion is bound to result, and particularly in considering the afferent or sensory side. The author deploras particularly the extension of the visceral afferent conception to the study of the special sense organs which arise in the ectoderm.

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**Influence on the Boundaries of the Pleura by the Inferior Sternopericardial Ligament.**

*E. Sturzenegger and W. Willi, Anat. Anz., Jena, 56:134, Sept. 30, 1922.*

A man of 40 showed a clearly defined strong band of connective tissue passing from the anterior surface of the pericardium to the under side of the xiphoid process of the sternum. The anterior line of transformation of the sternocostal pleura into the mediastinal pleura formed 2 pockets, an upper, ventral one, only slightly developed in front of the ligament between it and the sternum, and a lower, more strongly developed one behind the ligament, between it and the pericardium. Neither of the pockets contained lung tissue and the lower one was greatly indented by fat flaps. An abnormally persistent thymus had probably caused the separation of the pleural boundaries on both sides.

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### **Morphology of the Human Cecum.**

*E. Jakobshagen, Anat. Anz., Jena, 56:97, Sept. 30, 1922.*

The only animals that have a cecum with tenias and an appendix vermiformis without tenias are (1) the anthropoid apes, (2) the family Loris, among the lemurs, and (3) the family of the Australian wombat, among the marsupials. Kelly and Hurdon have shown for man that the cecum-appendix articulation took place from arrested development of the base of a cecum that was at first undivided; the same thing has been demonstrated for anthropoid apes (hylobates). In these not only are the higher degrees of Treves' fold lacking, but the cecum-appendix articulation occurs much later than in man. Treves' fold is more prominent in oranges and chimpanzees, most so in gorillas. In the latter the shortest appendix is found. In the different specimens of Loris the beginning of the development of the appendix vermiformis can be clearly followed, until the Treves' second type is reached. In the wombat the asymmetric Treves' third and fourth types of cecum are regarded as stages in a cataplastic process which led to atrophy, first, of the dorsal half of the cecum, then of the appendix vermiformis, and finally initiated the retrogression of the ventral half of the cecum. In all cecums, Treves' fold is a stunting of the dorsal wall of the cecum. In man the fold is the same, only varying in size.

The questions now arise: Why in the appendix of man, the anthropoid apes, Loris and wombat are the tenias and haustrums lacking, and why do the tenias of the cecum unite to form a closed longitudinal mantle of muscle? Why is the caliber of the appendix so small, its length so variable? Why did the cataplasia of the cecum lead to the development of an appendix at all and not simply to a shortening of the cecum? The tenias are lacking in the large intestine of most mammals, and where they do occur it is only in highly differentiated forms of animals. Haustrums are present where there are tenias. The appearance of a tenia-haustrum-cecum in many groups of mammals shows an anaplastic step, the beginning of a differentiation from the older tenia-free time. Therefore it is natural that in the appendix vermiformis, which is the cataplastic part of the cecum, the older and simpler condition should be preserved, and the anaplastic tenia-haustrum formation should be lacking. The shorter diameter of the appendix is comprehensible when we remember that the cecum and the later appendix from the eighth week are greatly outdistanced by the growth of the large intestine. This inactivity probably affected the base of the cecum of our human ancestors and led to atrophy from inactivity.

The varying diameter of the appendix as well as its varying length is also a characteristic of other cataplastic organs. But this atrophy from inactivity should have led simply to a shortening of the cecum and not to the development of an appendix, which is often long. This problem cannot be solved. Moreover the mucous membrane of the appendix in man has in comparison with its surface an incomparably greater number of lymph follicles. This is probably due to the fact that only the follicular apparatus defied the cataplastic process. At any rate it is impossible not to recognize the cataplastic character of the human appendix. A metaplasia of an organ on the descending path of development, by the formation of a lymph system in the appendix, is

not demonstrated. Among the apes the platyrrhines have longer cecums than the catarrhines. The long cecum of the prosimians that survive today is a palingenetically inherited reminiscence of our racial history.

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**On Truncated Umbilical Arteries in Some Indian Mammals.**

*Basanta Kumar Das, J. Anat., London, 56:325, April, July, 1922.*

Woodland having described as a unique anatomic fact the blindly ending umbilical arteries of the common Indian goat, the author examined 28 species of Indian mammals to ascertain if this finding was the rule in India. In 26 of the species examined truncated umbilical arteries were found to exist. These can be roughly separated into 2 groups: (1) those of approximately uniform diameter from their origin to their extremity, and (2) those in which the diameter diminishes to some extent toward the extremity. Arteries of Group 1 type were found in the very young domestic pig, the buffalo, bullock, blue bull, bazaar cat, panther, Gangetic dolphin, adult pariah dog, common brown monkey, Indian fruit-bat, mustachioed bat, Indian horse, ass and sheep. Arteries of the Group 2 type were found in the doe of Antelope cervicapra (black buck), in the langur or hanuman monkey, hare, palm-squirrel, porcupine, Indian wild boar, jackal, Indian fox, Indian palm-civet, and the common Indian mongoose. The histologic features of the truncated umbilical artery are: (a) the lumen is much smaller relative to that of such a normal artery as the internal iliac; (b) as a general rule the walls are thicker (absolutely) than those of the internal iliac arteries; (c) posteriorly the lumen of these vessels gradually narrows and becomes broken up into small intercommunicating spaces, which finally terminate toward the tip, the center of the artery being occupied with a core of muscle. The author believes these umbilical arteries are merely conspicuous embryonic vestiges and have no particular function; this view is supported by the fact that in young mammals they are very much larger, relative to the internal iliacs, than those of adults, the lumen in the adult umbilical artery being much reduced in size.

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**Reproduction in Cell Communities.**

*T. Brailsford Robertson, J. Physiol., London, 56:404, Oct. 18, 1922.*

The author has made further experiments upon the accelerative effect which infusoria have on one another. He has already shown that when pairs of infusoria (*Enchelys farcinem* Ehr.) are isolated into the same drop of culture medium, the rate of new cell production is much more rapid than it is when a single individual is isolated into a drop of the same size. This "allelocatalytic" effect is clearly shown by the increase in reproduction rate which is brought about by mere reduction in the volume of the culture medium, the smaller the volume of culture medium into which a single infusorian is isolated, the greater is the initial multiplicative rate of the culture. Distilled water, to which a proper reaction and tonicity have been communicated by the

addition of a buffer mixture of phosphates, and which has been densely populated by dividing infusoria, contains a substance which enhances the multiplicative rate of isolated infusoria. The autocatalytic character of reproduction of cultures of infusoria is attributed, partly to the inherent capacity of each cell to reproduce itself, due to the presence within it of a catalyzer capable of effecting protoplasmic synthesis, and partly to the shedding of a catalyzer into the surrounding medium, through the agency of which the cells mutually are enabled to facilitate reproduction. An isolated cell placed in a nutrient medium displays a period of inertia or "lag" before it responds to the stimulus of abundant foodstuffs by reproduction of its kind. The acceleration of reproductive rate is observable only after division of the isolated cell.

The author proposes the hypothesis that during the periods between nuclear divisions each nucleus retains the charge of autocatalyst with which it was originally provided, and adds to it in the course of the nuclear synthesis which is rendered possible by its presence. At the next division the autocatalyst is shared between the nuclear materials and the surrounding medium in a proportion determined in part by its relative solubility in the 2 mediums, and in part by its affinity for chemical substances within the nucleus. At the end of this redistribution the autocatalyst stands in equilibrium between the external solvent medium, on the one hand, and, on the other hand, the nuclear substances with which it is combined or in which it dissolves. The nuclear membrane is then re-formed, and the autocatalyst within the nucleus is again shut off from dispersal.

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**Early Development and Placentation in Arvicola (Microtus) Amphibius, with Special Reference to the Origin of Placental Giant Cells.**

*G. S. Sansom, J. Anat., London, 56: 333, April, July, 1922.*

In this work wild water voles were killed during the months of March and April when their first breeding season occurs. The ovaries and uteri were removed immediately after death and placed in fixing fluids (Bouin's picroformol acetic; alcohol sublimate-acetic mixture). The ovaries and uteri were cut in sections 5, 8 or 10 microns thick. A study of 27 figures which accompany the article shows that the implantation cavity early becomes surrounded by a belt of maternal capillaries, the endothelial cells of which exhibit characteristic changes. These cells become phagocytic giant cells. The decidual tissue adjacent to them breaks down with the formation of symplasma masses, which are re-absorbed by these giant cells. All the placental giant cells are of maternal endothelial origin. The ectoplacental trophoblast does not appear to be actively phagocytic. Its penetration is assisted by the giant cells, which destroy the decidual tissue in its line of advance. Around the antimesometrial end and lateral walls of the implantation cavity, the giant cells form a vascular network in contact with Reichert's membrane. This network serves to facilitate the rapid stretching of the capsularis which results from growth of the embryo. The ripe placenta is of the discoidal, hemochorialis type, the maternal blood circulating in syncytial trophoblastic lamellae, subdivided by fetal mesenchymatous villi, carrying allantoic capillaries. The yolk-sac splanchnopleure does

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not come into contact with maternal tissues until, or very shortly before, parturition. It is always separated therefrom by the persistent Reichert's membrane.

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**The Different Forms of the Spinous Process of the Axis in Their Relations to the Musculature.**

*F. Kasche, Anat. Anz., Jena, 56:169, Oct. 16, 1922.*

The spinous process of the human axis is distinguished by a great variety of forms. There is some question as to the relations between the form of the spinous process and the attached musculature. The muscles are the part of the transversospinal muscle attached caudally to the axis, and the rectus capitis posticus major and the obliquus capitis inferior which pass toward the head from the spinous process of the axis. There is no relation between the strength of the 2 latter and the form of the process. The transversospinalis muscle divides into the semispinalis cervicis and the multifidus. The insertion of the latter extends over the process to the arch of the vertebra. There are 2 extreme forms of insertion, one limited to the process almost from the apex to the root, another reaching into the lower joint process. This muscle which has a narrow insertion often lies around the semispinalis like a sheath and more or less clearly delimited from it; this also occurs now and then with the multifidus, which has a broad insertion. If the insertion is limited to a small area it will exercise a stronger traction in the caudal, ventral and lateral directions than if the insertion is broad and band-shaped. Between the typical extreme conditions there are numerous transitional forms. The narrow form of the axis spinous process and the insertion of the multifidus at the arch of the vertebra are primitive forms.

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**The Finer Structure of the Epithelial Muscle Cells of Hydra Grisea and Fusca.**

*Er. Roskin, Anat. Anz., Jena, 56:158, Oct. 16, 1922.*

In the body of Hydra there are 2 kinds of muscle fibers: (1) longitudinal muscle fibers which belong to the ectoderm cells and (2) circular muscle fibers which belong to the entoderm cells. Every epithelial cell has 2 processes. The muscle cell fibers course along the supporting lamellae and fine, pseudopod-like plasma processes project into the gelatinous supporting substance. The length of the muscle cell processes may reach 0.38 mm. By the use of some staining methods the muscle cord in the muscle cell process can be sharply demonstrated. With Benda's stain (toluidin blue and alizarin sodium sulphate) the muscle cord appears blue in the midst of red protoplasm; with Mallory's stain the muscle cord is colored dark blue, the protoplasm violet and the nucleus reddish yellow. With all stains the muscle cord stains very densely and therefore appears opaque. The muscle cord is a long cylindric column which consists of two layers: an envelope, which exists in a firm state of aggregation and forms the cylindric sheath or membrane of the muscle cord and a very refractive plasma. The

latter is the actual contractile part, the kinoplasm. The form of the fibrils is determined by their membranes. There may also be skeletal fibers which cannot be distinguished in the kinoplasm column which has become very opaque by deep staining. After maceration in 1% acetic acid the middle part of the muscle cord swells and in the terminal part the plasma breaks up into small droplets which hang together in a thin thread. The skeletal fibers in comparison with the cytoplasm are more resistant to acids and alkalis. The elastic skeletal fibers serve for morphologic regulation of the movement of the muscle cell. The muscle fibers of the entoderm cell are distinguished by their comparatively smaller diameter. In the entoderm of the hydra there is a series of cells which are sharply distinguished from the ordinary cell by the special characteristics of their muscle cord. This is very thin and gives the impression of a solid structure. It is not possible to find a kinoplasm or a membrane; the muscle cord corresponds to a skeletal fiber. These entoderm cells serve to preserve the form and dexterity of the organism of the hydra. The name "epithelial supporting cells" is proposed for these cells.

## ABNORMITIES

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### Parabiosis.

*Werner Schulze, Klin. Wchnschr., Berlin, 1:2007, 2052, Sept. 30, Oct. 7, 1922.*

Sauerbruch and Heyde have joined young animals so that a union of the 2 organisms into a single whole resulted. Although the biologic individuality of the 2 organisms was preserved, extensive correlations were established; hence the condition was called parabiosis. Schaxel proposed the term "implantation symbiosis." The fundamental question in parabiosis is how far the biologic individuality of each organism is preserved or decreased through anatomic union.

The union of 2 organisms into an anatomic whole, with possibly physiologic fusion as well, constitutes regressive regeneration. In contrast to this, there is simple regeneration, in which the separated halves of an original whole may again be joined to form a complete organism. The physiologic correlations of a xiphopagus or a pygopagus, e.g. Siamese twins, are similar to those of parabiosis. Every union of ovum and spermatozoön might be conceived as parabiosis, and the relation of the female animal to her fetus might be considered as homoplastic parabiosis of 2 unlike organisms. In parabiosis of mature animals the biochemical difference is greater with increasing age, leading to inharmonious parabiosis or spontaneous separation of the 2 partners. In like manner, with increasing development of the fetus, there is an accumulation of material in the maternal organism which leads to separation (birth). In both of the foregoing instances there is a transmission of passive, but not of active, immunity. It is necessary in parabiosis, as in transplantation, to differentiate the 4 periods of Roux, which characterize the course of individual life. In both cases, there is a decrease of ability for complete fusion with ascending species, and increase of the heterogeneity between species with advancing age of the individual. The

most highly differentiated tissues (nerves) are not able to unite in either procedure.

By stripping the membrane from the sea urchin eggs and by light scarification of the surface of the eggs, it is possible to bring about union of the larvas up to the blastula stage. If the blastulas are old, double development takes place. With younger larvas, there is fusion into a complete whole, the stronger developing to a higher degree at the expense of the weaker. When the embryos are united very young, a complete single individual develops, being twice as large as the normal, because composed of twice the number of cells. If an organism in the first developmental phase of Roux is united with one in the third phase, the biologic individuality of each organism is completely retained; if the younger organism is sufficiently developed, it separates. Belogolowy placed fertilized eggs of the frog in the abdominal cavity of adult animals. The eggs died owing to lack of oxygen and to the resorptive activity of the peritoneal epithelium. In many places the cells composing the embryo united with abdominal organs, grew and multiplied, thereby causing the death of the host by tumor growth. The biologic individuality of the cell elements of the 2 partners was preserved. The results, however, led Born to believe that the eggs were completely absorbed and that the tumors represented reactive growth of the host's own tissues.

Born united parts of 2 larvas from different eggs to make a third complete individual and from this drew the conclusion that the individual is not bound to a descent from one egg. The agglutinated amphibian larvas may be more or less adherent to each other, but always the biologic individuality of each member is preserved to the extent that each develops independently except for the common parts. After fusion of the 2 intestinal anlagen both animals develop to the same extent. After fusion of the heads, both larvas may have the same size in the beginning, but one may outgrow the other, and the latter may atrophy secondarily. But despite the small size of these stunted individuals their development advances equally if only the vascular systems anastomose. Even when the larvas have large parts of the brain in common, there is still a separate innervation, the individuality of the two being absolutely preserved with reference to response to stimuli. While epithelial and connective tissues fuse directly, more highly differentiated nerve tissue in spite of morphologic union does not undergo physiologic union. Experiments in parabiosis on warm-blooded animals made by Sauerbruch and his students showed features in common with the experiments on cold-blooded animals. In senility, parabiosis no longer succeeds, nor does heteroplastic parabiosis with animals of a different species. Injected rabies or tetanus toxin never passes into the nerve tracts of the other partner. The exchange of material takes place through the lymph tracts, the capillary regions anastomose, but rarely the larger vessels. On long continuation of the union sometimes one animal shows excessive growth and the other becomes pale, thin and anemic, the hair becomes rough, and the animal dies. This process is interpreted as athrepsia or as an increase of the biologic difference with hemolytic action of the serum of the larger animal on the blood of the smaller one. If one animal becomes pregnant reactive changes occur in the partner. Shortly before labor the nonpregnant partner, even though a male, becomes feeble and sometimes dies. If one of the animals dies, the other does also if they are not promptly separated. Drugs, toxins and vital

stains pass from one partner to the other, and passive immunity acts on the other animal, but appears later and is weaker. For active immunization of both larger amounts of antigen must be administered to one. Bacteria pass from one to the other. Ligation of the intestine of one animal produces later symptoms of ileus in the other; the blood and tissues are sterile in the second animal, proving that toxins and not bacteria cause the symptoms. Extirpation of 1-3 of the 4 kidneys of the animals leads to compensatory hypertrophy and hyperplasia of the remaining kidney. After extirpation of both kidneys of one animal uremia may not set in for a long time, but it always occurs, probably from accumulation of intermediate products of metabolism. Pancreatotomy leads to glycosuria in an individual animal, but in parabiotic animals the injury is attenuated or its action delayed. Adrenalectomy in one animal is compensated by the suprarenals of the partner; after extirpation of the sex glands there is vicarious hypertrophy of the testicle, seminal vesicles and prostate of the other partner. When a female animal is united with a castrate, after initial hypertrophy and hyperfunction of the ovaries and the development of numerous corpora lutea, cystic degeneration occurs.

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**A Two-Headed Calf.**

*Edward B. Benedict, Boston M. & S. J., 187:639, Nov. 2, 1922.*

The calf had a single trunk and 4 legs, but its 2 spines, though gradually converging, remained separate throughout and ended in 2 distinct tails. The 2 necks converged and joined externally at about the midcervical region. Internal examination revealed complete or partial doubling of the respiratory, cardiovascular, and gastro-intestinal systems. The lateral forelimbs were normal, but the median pair were represented by a broad, cartilaginous plate, evidently derived from fusion of 2 scapulas. This was packed in between the 2 spines. Deep within the muscles at the root of the neck, and thus at the upper end of the thoracic cavity, was a spherical cyst, thickly lined with white hair. The double scapula and the dermoid cyst were the only indications of the median pair of forelimbs. The calf was the fourth offspring of a large pure-bred Holstein cow and bull; the other 3 calves had been normal. Delivery was difficult and the calf did not live.

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**Congenital Absence of the Spleen.**

*Stafford McLean and Howard R. Craig, Am. J. M. Sc., 164:703, Nov., 1922.*

This is one of the rarest of all visceral anomalies. It occurs as a single abnormality, but more frequently is associated with one or more congenital malformations. In all the reported cases it was an accidental discovery at autopsy. Some of the cases occurred in infants, others in adults, who at no time showed symptoms referable to the absence of an important viscus.

A boy, aged 3 months, was brought to the hospital because he did

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not thrive. Symptoms noted by parents had been "cold in the head" associated with fever up to 103° F. for a week, and rapid respiration on the day prior to admission. There was some dyspnea and the skin of the entire body was slightly cyanotic. He continued to lose weight and fever fluctuated between 100° and 102° F. Both ear drums were incised and pus obtained. Infant was removed from hospital 19 days after admission; 2 days later severe respiratory symptoms developed and he died. Autopsy findings were congenital absence of spleen, congenital malformation of heart, lungs and liver, atelectasis and bronchopneumonia.

This case, as well as others found in the literature, may be of some value in determining the importance of this organ. In 9 cases collected the individuals with this anomaly reached middle life without recognizable disturbance; 1 woman, who had had 4 normal pregnancies, died at the age of 73. In 7 of the adult cases there was no lymphoid hyperplasia, while in 2 there was definite lymphoid hyperplasia, which was termed compensatory by the writers. In the authors' case and in 4 others in infants there was apparently no hyperplasia of lymphoid tissue. The conclusion is justifiable that in certain individuals, congenital absence of the spleen is apparently not a serious handicap.

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**An Unusual Malformation of the Heart.**

*Tsing Yü, Anat. Anz., Jena, 56: 134, Sept. 30, 1922.*

On both sides of the midline was a large vein which arose bilaterally from the confluence of the subclavian and jugular veins, extended downward almost perpendicularly and emptied into the heart posterior to the large arteries. There was no connection between these 2 vessels; a large inferior thyroid vein emptied into the right vein. On sounding and opening the heart cavity it was found that the end of the left superior vena cava ran toward the right for a distance in the cranial wall of the auricle, so that the orifices of the 2 superior venae cavae lay very close to one another. Moreover there was no eustachian valve of the inferior vena cava; there was no thebesian valve nor any coronary sinus in the coronary sulcus. The auricles on the 2 sides communicated by a wide opening; the only traces of the auricular septum were in the shape of a low ridge of muscle.

GENERAL PHYSIOLOGY

(1a—417)

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**A Substitute for the Long Roll Kymograph.**

*Felix P. Chillingworth, J. Lab. & Clin. Med., 8: 52, Oct., 1922.*

This drum fits accurately the Harvard kymograph motor, and, having a circumference of 90 cm. and a height of 30 cm., gives a greatly increased area of smoked writing surface. The ends of the drum are made of light wood, through which the sleeve passes. The height of the drum permits the use of a wide kymograph paper which has the advantage that by an adjustment upward or downward of the drum, the writing point level can be readily changed, which does away

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with the usual method of either raising or lowering the kymograph in its entirety, or of raising or lowering the recording apparatus. This simple adjustment is brought about by a rack and pinion, the rack being soldered on the sleeve of the drum; this allows the drum to move instantly in either direction. The lower end of the sleeve is covered by a brass bushing sufficiently high to permit the base of the drum to just clear the governing fan. For some speeds it is desirable to increase the fan surface.

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**Golgi's Internal Apparatus in Different Physiologic Conditions of the Mammary Gland.**

*C. Da Fano, J. Physiol., London, 56: 459, Oct. 18, 1922.*

Soon after the publication of his arsenious acid and silver nitrate method, Golgi gave a description of the apparatus of the mucus secreting cells of the gastric and intestinal epithelium of various vertebrates. De Fano undertook this research to determine if one or more of the changes of the apparatus described by various workers could be observed in epithelial cells undergoing some well-defined functional modification. The greater part of the experiments was made on mammary glands of mice and rats, which are easily obtained at known periods of pregnancy and lactation. Material for comparison was collected from cats, rabbits and guinea-pigs, of which the age and functional condition had been at least approximately ascertained. All the glands were fixed and treated according to the author's cobalt nitrate method. The work included a study of the mammary gland of very young animals, of pregnant animals, of lactating animals and of animals during the period of involution after lactation.

The author found that Golgi's internal apparatus is a constant feature of the epithelial cells of the mammary gland in all stages of their physiologic history. In the virginal condition the apparatus consists of one or more small reticular portions situated next to the nucleus on the side facing the glandular lumina. During pregnancy the apparatus greatly hypertrophies and shows a tendency to surround the nucleus with its network. This phenomenon appears to be brought about by the approaching hyperactivity of the cytoplasm. From the moment the young are born and throughout lactation the apparatus is still hypertrophic, in part fragmented and shifted and stretched in various directions. During involution after lactation the epithelial cells undergo deep changes during which the apparatus appears to become transformed into peculiar roundish, oval or elongated shapes delimited by a granular or filamentous argentophil material. Most of these cells are eliminated with their deformed apparatus. Some remain as the permanent epithelium of the gland at rest and in these cells an apparatus is found similar to that of the virginal condition. Regarding the mammary gland, the author observed nothing favoring the supposition that part of the apparatus is thrown off from the cells together with other products of their secretory activity, but the continuous passage of detached epithelial cells, with their apparatus, into the glandular lumina and ducts is assumed to mean that in this way the apparatus takes an indirect part in the function of the gland.

CIRCULATORY SYSTEM

(1a—419)

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**Vasoconstrictor Substances in the Blood.**

*Walter Huelse, Klin. Wchnschr., Berlin, 1:2140, Oct. 21, 1922.*

In unfolding its action adrenalin is consumed in the tissues so that it does not enter the peripheral venous blood. Vasoconstrictor substances capable of simulating adrenalin are produced as a result of blood coagulation. Arterial and venous blood of different hypertonias was investigated by the frog transfusion method as regards its vasoconstrictor effect and the fate of adrenalin in the body was examined. Fresh human venous blood (citrate blood) causes no increase in the velocity of transfusion; the added suprarenin was present in full concentration even half an hour later. Also, fresh arterial citrated blood from individuals with normal blood pressure contained no vasoconstrictor substances although the preparation was sensitive to adrenalin dilution of 1:3 billions. The vasoconstrictor power of arterial blood is, therefore, less than that of a suprarenin dilution of 1:1.5 billions. The same negative result was shown by arterial blood in hypertension. But in blood pressure increased artificially by suprarenin injection, suprarenin is detectable in arterial blood even with such small amounts as have led to no increase in blood pressure. The threshold for the latter lies at a concentration of 1:200 billions or 1:300 billions in arterial blood. In peripheral venous blood suprarenin was never detected.

Physiologic adrenalin can be followed in the rabbit as far as the right heart but is not detectable in the left heart and has, therefore, already undergone destruction in the lung. This destruction, however, affects only about one half of an injected suprarenin volume so that normal arterial blood may also be assumed to contain adrenalin. Adrenalin, therefore, has to fulfil important physiologic functions in the body. Morbid increase of blood pressure is not conditioned by an increase of vasoconstrictor substances in the blood and particularly not by adrenalin.

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**The Utilization of Oxygen in the Blood at Different Stages of Anoxemia.**

*Carl H. Greene and Charles W. Greene, Am. J. Physiol., 62:542, Nov. 1, 1922.*

In a previous article the authors reported the changes in the oxygen content of the arterial blood of dogs during progressive anoxemia. They now record the corresponding changes in the venous blood, based on analyses made coincidentally with those of the arterial blood. The object was to determine the changes in the utilization of oxygen from the blood, and if possible to associate these changes with the coincident compensatory changes in the circulatory and respiratory mechanisms. The experimental and analytical procedures employed were the same as those used by the authors in their previous work. The venous blood samples were drawn from the jugular vein at the same time that the arterial blood and the alveolar air samples were taken. The blood was drawn under oil, care being taken to prevent stasis. The venous samples

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were analyzed immediately in duplicate by the Van Slyke blood-gas apparatus and method. In a second series the alveolar oxygen sample was taken from a sound inserted deep into a bronchus.

The authors found that the utilization of oxygen from the blood is nearly constant, and is independent of the arterial oxygen tension until the venous oxygen reserve is exhausted. Thereafter, the oxygen utilization parallels the saturation of the arterial blood. Respiratory and circulatory crises occur at the approach of the point at which the arterial saturation is reduced below the normal level of oxygen utilization. The oxygen tension of the alveolar air does not materially affect the blood flow until the crisis is approached. The blood flow and the oxygen utilization may show minor changes secondary to changes in the blood pressure or in the condition of the animal. The authors observed no significant change in the blood flow as a direct result of the anoxemia.

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**A Phenomenon Observed after Intravenous Injections of Oxygen in Some Experimental Animals.**

*Luigi Torraca, Riforma med., Naples, 38:985, Oct. 16, 1922.*

The findings noted by the author may be thus summed up: Following injection into the jugular vein of an animal (guinea-pig or dog) of a volume of oxygen in excess of that which can be readily dissolved in the blood, the oxygen passes through the pulmonary circulatory system in a gaseous state, reaches the left ventricle and is thence distributed into the general circulation. If the introduction of oxygen into the blood is continued the gas escapes from the blood vessels and collects in the peritoneal cavity and, in the guinea-pig, also in the intestinal tract, although to a much lesser extent. This phenomenon is strictly limited to the peritoneum; none of the other serous membranes nor any other tissue, not even the subcutaneous connective tissue, shows the least trace of accumulation of gas or the slightest indication of emphysema. The occurrence of the phenomenon is not easily explainable. One may assume that the passage of oxygen from blood vessels into the peritoneal cavity is perhaps rendered possible by special pressure conditions within the latter structure.

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**Erythropoiesis in the Hypophysis of the Human Fetus.**

*Petru Galesescu, Spitalul, Bucharest, 42:255, Sept., 1922.*

The hypophysis of the human fetus by certain microscopic methods presents a picture similar to that of erythropoiesis in the fetal liver and pancreas, particularly in its outer part, which consists of a dense network. The formation of red blood-cells from epithelial cells can be followed step by step in barely perceptible transitions. The author comes to the conclusion that the capacity for internal secretion is partially identified with the capacity for erythropoiesis and that many endocrine glands also play a part in erythropoiesis before they produce internal secretion in the strict sense of the word.

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**Blood Destruction during Exercise. 1. Blood Changes Occurring in the Course of a Single Day of Exercise.**

*G. O. Broun, J. Exper. Med., 36:481, Nov. 1, 1922.*

These investigations were undertaken in order to determine whether an increased rate of blood destruction during exercise could be demonstrated. Adequate data could be obtained only by accurate estimations of cell and plasma volume during the course of the experiments. The vital red method of blood volume determination was employed, the technic following that described jointly by Hooper, Smith, Belt and Whipple, and by Smith. Vital red was used in 1% strength for injection; dogs weighing 10-15 kg. received 4 c.c., while those above 15 kg. received 5 c.c. The hematocrit readings were made by filling 3 tubes of the Epstein type from each specimen of blood and centrifugalizing at 3500 revolutions for 30 minutes. The average plasma percentage of the 3 tubes, after correction for oxalate dilution, was taken as the true plasma percentage of the blood. Hemoglobin determinations were made by Newcomer's method. Red cell counts were made in duplicate from the oxalated blood of the jugular vein. Hayem's fluid was used and the Bürker-Zeiss counting chamber.

The chief reason for selecting dogs for the experiments was the special susceptibility of their red cells to mechanical injury. For purposes of exercise, treadmills were used, so constructed that the tread was at an angle of 20° to the horizontal. The standard day's exercise consisted of 2 periods of 2 hours each, separated by 1 hour's rest. The 12 complete experiments were carried out during warm weather and panting was regularly induced in the animals.

Analysis of the experimental data shows that 10-15 minutes of active exercise usually caused a slight increase in plasma volume and a marked increase in cell volume, hemoglobin, pigment volume (product of the blood volume by the per cent of hemoglobin), and number of corpuscles per cubic millimeter. This probably results from a redistribution of red corpuscles, with an increase in their proportion in the peripheral blood. After several hours' exercise, the plasma volume shows consistently an increase, the average rise above the resting normal being 11.7%; on the other hand, cell volume, while remaining at an average of 9.4% above the resting volume, shows an average decrease of 2.9% below the average found at the end of 10 minutes' exercise. The tendency of the hemoglobin per cent to decrease is more marked but this is partly due to dilution of the blood by increase in plasma volume. The calculated pigment volume, with the error of dilution corrected, shows after the period of prolonged exercise a 7.7% fall below the average after 10 minutes of exercise. The final average pigment volume is 8.4% above the average of the first determination. The coincident decrease in both the total cell volume and the pigment volume during prolonged exercise suggests that blood destruction then occurs. Although the animals used as controls were kept in small cages throughout the period of observation, it was not possible to prevent a certain amount of activity on their part. Nevertheless the findings in these control animals were in striking contrast with those of the exercise series. There was an average increase of 4.6% in the second plasma volume over the first, close to that in animals exercised for 10 min.

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**The Influence of Water Introduction upon Blood Concentration Induced by Water Deprivation.**

*Frank P. Underhill and Robert Kapsinow, J. Biol. Chem., 54:459, Oct., 1922.*

This investigation was undertaken to determine the influence of water deprivation for relatively short periods upon alterations of blood concentration, as well as the effect of the introduction of large volumes of fluid upon the changed blood concentration. The experimental procedure consisted in keeping well nourished adult dogs in metabolism cages without food and water for periods varying from 5 to 8 days. During this interval blood concentration changes were followed 3 times daily by estimation of hemoglobin content of blood (method of Cohen and Smith) obtained by puncture of an ear vein. Urine volume was determined daily by catheterization. When blood concentration had seemingly reached a maximum water was offered and the animals allowed to drink until satisfied. Hemoglobin estimations were then made at short intervals. The authors' graphic results show that short intervals of water deprivation significantly increase the blood concentration of dogs. Water introduction in animals with concentrated blood produces a return of blood concentration to a point approximating the normal.

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**Hematoidin.**

*Hans Fischer and F. Reindel, Münch. med. Wchnschr., 69:1451, Oct. 13, 1922.*

As is shown in Aschoff's work (SURVEY, Nov., 1922, 1a—356), it is of great importance to determine whether bile-pigment can develop outside the liver directly from hemoglobin. The author demonstrated conclusively from extensive experiments that hemoglobin is transformed into bile-pigment and bile-pigment derivatives with splitting off of albumin and iron, which, in confirmation of the findings of older authors, together with hematoidin was found partly in ionized form, partly in organic compounds. Hence it is possible for icterus to develop without involvement of the liver, as has already been found by Aschoff in animal experiments. Urobilinuria without involvement of the intestinal tract also seems theoretically possible.

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**The Activity of the Spleen in Bilirubin Formation.**

*Arnold Rice Rich, Klin. Wchnschr., Berlin, 1:2079, Oct. 14, 1922.*

The present experiments sought to produce such a degree of hemolysis in normal and splenectomized dogs as would suffice to force all bilirubin forming depots to their maximum activity. If the spleen plays an important rôle in the production of bilirubin, splenectomized animals should excrete less bilirubin in the bile than normal ones. In order to attain the most constant degree of hemolysis possible, and a corresponding constant increase in bilirubin excretion, the experimental



animals received injections of a definite quantity of distilled water per kg. body weight. Histologic examination of the livers, made from 3 hours to 2 months after the injections, showed that the liver-cells were vacuolated in varying degree and extent, while the nuclei remained normal. During the first 24 hours after the first injection the animals excreted 1.5-1.7 times the average normal amount of bilirubin, after the second injection 1.4-1.6, and after the third injection 2.5-2.8. If the spleen really plays an important rôle in the formation of bilirubin under physiologic conditions, it should be possible to prove this fact by comparing the above results with those obtained in splenectomized animals. It appeared that, under the same hemolytic conditions, there was a similar increase in the excretion of bilirubin in the splenectomized animals. The more marked increase after the second and third injection was also demonstrated. To determine whether there is a difference in the bilirubin content of the splenic vein and peripheral blood, the author applied van der Bergh's method and found both serums free from bilirubin. In three experiments, following hemolysis, bilirubin was found in the serum of the spleen, carotid artery and jugular vein. Only in one case did the splenic vein contain more bilirubin than the peripheral blood. At all events, these experiments do not support the view that the spleen forms bilirubin. The spleen is wholly unnecessary for the conversion of the hemoglobin from the blood-corpuscles into bilirubin.

## DIGESTIVE SYSTEM

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### **Comparative Studies of Digestion.**

*Meyer Bodansky and William C. Rose, Am. J. Physiol., 62:473, 482, Nov. 1, 1922.*

*Digestive Enzymes of Coelenterates.*—The present investigation is limited to 2 species of coelenterates, the first a large medusa described by Agassiz as *Stomolophus meleagris*, the second the siphonophore *Physalia arethusa*, commonly known as the Portuguese-man-of-war. Fresh tissue suspensions were made from both species and for the identification of the proteolytic enzymes in the coelenterates, gelatin solutions of definite concentration were digested at 37° C. by the tissue suspensions. At stated intervals measured portions of the digests were removed and the progress of the digestion determined. Evidence of fat digestion, as determined by the litmus milk test, was obtained with the tissue suspensions. The presence of a lipolytic enzyme capable of slowly hydrolyzing ethyl butyrate and amyl acetate was also observed. In addition the authors found in *Physalia arethusa* and *Stomolophus meleagris* the following digestive enzymes: pepsin, trypsin, rennin, amylase and maltase. Invertase was present in negligible quantity.

*Digestion in Elasmobranchs and Teleosts.*—In this investigation the authors compared the digestive action of the pepsin of fishes with the effect produced by commercial pepsin. For this purpose, gelatin was employed as the substrate, the digestion of which by the pepsin was investigated in 3 species of elasmobranchs, i.e. shark or dogfish, sawfish, and the torpedo ray. The Dernby method, previously used by the authors in the study of proteolytic digestion in coelenterates, was employed in this investigation. The gastric mucosas of 2 sharks

(*Squalus acanthias*) were scraped and triturated with toluene and water, the extract filtered and 1 c.c. of the filtrate was used in each of the tests. Experiments were performed with the extracts prepared from the gastric mucosas of the other elasmobranchs and from 4 species of teleosts, i.e. red snapper, flounder, cowfish, and the black grouper. As in the shark, maximum peptic digestion of gelatin always occurred about pH 3.0, the hydrogen-ion concentration regarded as the optimum for mammalian pepsin.

For the purpose of studying the proteolytic enzymes, the glycerol-water extract, 60 c.c. in volume, was prepared from the cecal mucosas of 15 red snappers. One cubic centimeter of the resulting preparation was used in each of a series of gelatin tests. The tabulated results indicate the presence of a peptic as well as a tryptic enzyme. The authors confirmed this by a number of digestion experiments in which beef, fish fibrin, casein and coagulated egg albumin were used. In the extracts of the pyloric appendages of the red snapper, weak lipolytic action was detected with the ethyl butyrate and litmus milk test. The presence of maltase or lactase could not be detected in these appendages. Invertase occurred in minute traces. The stomachic sac of the torpedo ray secretes a rennitic enzyme which is absent in the dogfish and sawfish. Some teleosts (red snapper, flounder, and catfish) were observed to possess gastric rennin, which was not present, however, in the cowfish and mullet.

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#### **Occurrence of Free Acid in the Digestive Tract of *Oligochaeta*.**

*Edmund Nirenstein, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:60, Sept. 27, 1922.*

While an acid-secreting intestinal section has been met with in all vertebrate animals with the exception of some families of Teleostei, no analogous finding is recorded in invertebrates. In the microscopic oligochaetous *Chaetogaster diaphanus*, the intestinal part adjacent to the esophagus is divided into two saccular sections connected by a short intestinal piece whose structure resembles that of the esophagus. The anterior section is regarded as the stomach. The second section, the true middle intestine, contains resorptive parts furnished with cilia and vacuole inclusions filled with granules and fat drops as well as gland cells with acidophil granulation and basophil plasma. In the stomach only one kind of cell is found, which has a flat or cubic form, a homogeneous appearance and is free from considerable inclusions. The cells are characterized by long, rigid, bristle-like structures. The functional behavior corresponds to the morphologic differences. With Congo red and dimethylamido-azobenzene, free acid was demonstrated in the stomach section. This acid does not have a digestive action, as was shown by experiments with stained fibrin flakes, stained or unstained coagulated albumin and observation of the digestion of normal food. The ingested organisms are, however, destroyed in the stomach. To determine whether this is due purely to the acid, its strength was determined by the indicator method, the minimum concentration being found at 0.05 n. This concentration suffices for a destructive effect. Attempts to gain an insight into the process of acid formation by means of the

transparent object miscarried. No cellular portions with acid reaction were found. The acid-secreting elements appear homogeneous in vivo and in section so that the secretion of acid does not seem to be confined to any determinable structure. The gastric vascularization is very profuse.

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**Gaseous Interchange in the Stomach in the Anesthetized Animal.**

*Nora Edkins, J. Physiol., London, 56:421, Oct. 18, 1922.*

The object of these experiments was to determine whether there is any secretion or absorption of  $\text{CO}_2$  or  $\text{O}_2$  in the stomach. The observations were made on fasting cats that had been anesthetized. Various gas mixtures were introduced into the stomach cavity and restricted to it. After the desired interval the mixtures were removed and analyzed. Two hours after the introduction of 20 c.c.  $\text{N}_2$  the percentage of  $\text{CO}_2$  averaged 10 while the  $\text{O}_2$  percentage was greater than 0.65. Two hours after the introduction of 20 c.c. of a mixture of  $\text{N}_2$  and  $\text{O}_2$  there was a large gain of  $\text{CO}_2$  and a loss of  $\text{O}_2$ . When  $\text{N}_2$ ,  $\text{N}_2$  and  $\text{O}_2$ , or  $\text{N}_2$  and saline, were introduced into the fasting stomach, the  $\text{CO}_2$  reached a fairly constant level. Edkins concludes that the presence of  $\text{CO}_2$  is due to passive diffusion from the tissues of the wall of the stomach into the cavity. Since alveolar  $\text{CO}_2$  pressure was always found to be lower than gastric  $\text{CO}_2$  pressure and  $\text{O}_2$  pressure very much greater, the author believes it permissible to regard these experiments as comparable to the use of a tonometer for the purpose of gaging the tension of  $\text{CO}_2$  and  $\text{O}_2$  in the gastric mucous membrane. The conclusion may be drawn that the tension of  $\text{CO}_2$  in this tissue is greater than that of venous blood and that the tension of  $\text{O}_2$  is of a low order.

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**A Class Demonstration of Intestinal Activity.**

*A. E. Guenther and Homer C. Lawson, J. Lab. & Clin. Med., 8:60, Oct., 1922.*

This method requires the coöperation of 2 persons in the preparation for a demonstration. The animal is anesthetized preferably with a permanent anesthetic. Urethane is satisfactory for rabbits. After removing the abdominal hair an incision is made in the median line approximately  $4\frac{1}{2}$  in. in length, beginning 1 in. posterior to the tip of the xyphoid and involving the skin only. The skin is then loosened from the underlying abdominal muscle by separating the fascial planes. The dissection should extend about 1 in. anteriorly and posteriorly beyond each end of the incision and laterally  $1\frac{1}{2}$ -2 in. in both directions. An 8 in. ligature is now drawn through the adjacent right and left edges of the skin incision about  $1\frac{1}{2}$  in. from its anterior end and allowed to lie in place. An incision in the linea alba, opening into the abdominal cavity, should be made somewhat anterior to the center of the skin incision and not exceeding  $\frac{3}{4}$  in. in length. With caution a pair of forceps may now be introduced through the slit toward the animal's left and a loop of small intestine drawn upward and out through the incision.

With the fingers, previously moistened, 10-12 in. of the intestine may be gently drawn through the opening and allowed to rest on the exterior of the abdominal wall. If the intestines are empty and flat, it is desirable, at this time, to introduce hypodermatically, at various points along the loops, a small quantity of air.

A cylindric museum jar,  $3\frac{1}{2}$  by 7 in., and provided with flanges at base and top, is almost filled with Tyrode's solution which has previously been brought to body heat. A short thermometer, inserted into a cork to serve as a float, is placed in an inverted position in the jar. The assistant now grasps the forelegs and ears of the rabbit with one hand and the hind legs with the other and places the animal over the jar so that the intestines hang into the solution. While the assistant thus holds the animal in place, the operator draws the loosened skin over the flange of the jar and stretches it in place by means of the ligature mentioned above. It is now necessary to remove the layer of air separating the abdominal wall from the solution in the jar. To do this the operator inserts a rubber tube between the anterior edge of the incision and the jar, and by means of a funnel at the other end of the tube introduces warm Tyrode's solution which displaces the air. The jar and animal are rapidly inverted. The inverted jar is now held by a suitable ring support so that its weight and that of the contained fluid do not bear down on the body of the animal. The buoyant intestinal loops float up into the jar and can be viewed by a large circle of students. The effect is greatly enhanced by slightly darkening the room and illuminating the intestines from above by means of an incandescent light.

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**The Effect of Intravenous Sodium Bicarbonate on Intestinal Movements.**

*C. E. King and Jas. G. Church, Am. J. Physiol., 62:459, Nov. 1, 1922.*

The authors having on a previous occasion observed the violent response of the gastro-intestinal musculature of the dog to sodium bicarbonate intravenously administered, the present study was undertaken to ascertain more fully the type of the motor response of the small intestine of the dog to sodium bicarbonate, the factors affecting it and the mechanism involved. The observations were made on intact animals under ether and after decerebration, and with isolated segments suspended in oxygenated saline. The movements and changes in tonus of the intestine in the intact animals were recorded by the balloon-tambour method, the balloon being placed in the lower duodenum or upper jejunum. The strip movements were recorded in the usual way, suspended in oxygenated saline, fixed at one end and attached to a muscle lever by means of a silk cord at the other end. A study was made of the changes in both the circular and the longitudinal muscles. The authors' graphic results recorded in the article show that the intravenous injection of 50 c.c. of 2.5%, 4%, and 6% sodium bicarbonate into dogs brings about a vigorous motor reaction of the small intestine, the intensity of the reaction running somewhat parallel to the dosage. The authors found an increase in tonus to be the most constant feature of the reaction. Frequently local rhythmic movements appear, and

occasionally true peristalsis. The reactivity of the intestine is diminished after several successive administrations of sodium bicarbonate.

In seeking the probable nerve mechanism involved in the reactions described, the authors were able by experimental procedure to eliminate as causative factors (1) central stimulation of the vagus; (2) peripheral vagus stimulation; and (3) stimulation of the enteric plexus cells. The evidence as a whole indicates that the reaction of the small intestine of the dog to intravenous sodium bicarbonate is due to some factor acting upon the peripheral portion of the intrinsic nervous mechanism, possibly on the myoneural junction.

## METABOLISM

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### The Excretion of Acid and Ammonia.

*Roger S. Hubbard and Samuel A. Munford, J. Biol. Chem., 54:465, Oct., 1922.*

The data obtained by the authors on the above subject are based on a series of 21 experiments carried out on 19 subjects who did not show clinical or metabolic symptoms of acidosis. In each experiment specimens of urine were collected every 2 hours from 7 a.m. to 7 p.m., and a single specimen was collected from 7 p.m. to 7 a.m. of the following day. Practically all specimens were analyzed immediately. The determination of the hydrogen-ion concentration was carried out by a colorimetric method essentially the same as that recently described by Marshall; the titratable acid was determined by the method of Folin, and the ammonia by that of Folin and Bell. Gastric analyses were made by the fractional method of Rehfuess, Bergeim, and Hawk.

Resulting data embodied in the tables and charts show: (1) that ammonia excretion varied with the acidity of the urine; (2) that ammonia excretion varied with the volume of the urine excreted; (3) that the excretion of ammonia varied with the reaction of the urine, and that the amount of acid excreted did not directly affect its excretion; (4) that the agreement between changes of reaction and ammonia excretion was primarily between hydrogen-ion concentration and the concentration of ammonia, not between hydrogen-ion concentration and the amount of ammonia excreted; and (5) that large differences in volume led to a diminished agreement between the reaction and the concentration of the ammonia, while very small differences in volume sometimes were accompanied by concentrations which agreed more than the differences in the reaction would have indicated.

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### Nutrition on High Protein Dietaries.

*J. C. Drummond, G. P. Crowden and E. L. G. Hill, J. Physiol., London, 56:413, Oct. 18, 1922.*

The authors carried out experiments on young cats and rats to determine the effect of diets rich in proteins but containing in addition adequate amounts of salts and of the known accessory food factors. Control animals from the same litters were placed on normal diets. It



was observed that growth (though at a subnormal rate) was shown by the rats and cats fed on dietaries containing 80-90% of the dry weight in the form of protein (caseinogen), but apparently adequate as regards vitamins and salts. On changing to a normal diet the animals reached normal weight. The rats maintained excellent health throughout but did not reproduce while on the special diet. At the conclusion of the experiment the animals presented a normal appearance, while at autopsy the weight and condition of various internal organs did not differ from those of the normal controls. In the authors' opinion the failure of the animals to grow normally and to reproduce was due to a lack of balance between the protein constituent and some other component or components of a normal diet.

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**The Behavior of Amino-Acids in Vitally Stained Animals. I.**

*Y. Kotake, Y. Masai and Y. Mori, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:211, Oct. 6, 1922.*

The oxidative deamination of amino-acids in the rabbit organism is strongly diminished by so-called vital staining, so that no keto-acids can be detected in the urine even after copious administration of phenylalanin or tyrosin. A vitally stained rabbit excreted a relatively large amount of l-oxyphenylic acid in experiments with l-tyrosin. This probably justifies the assumption that the so-called histiocytic cells, particularly of reticular endothelium, play an important rôle in the oxidative deamination of amino-acids. The amino-acid, phenylalanin, was excreted unaltered in the urine. Soda-carmin was always employed. On examining one of the animals small carmin granules but no degenerative pictures were observed. In the central veins histiocytes filled with carmin granules were seen. Kupffer's stellate cells were much enlarged and rounded off owing to abundant carmin storage.

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**The Behavior of Amino-Acids in Vitally Stained Animals. II.**

*Y. Kotake, Y. Masai and Y. Mori, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:220, Oct. 6, 1922.*

According to researches by Embden and Baldes phenylalanin is partly converted into l-tyrosin in the excised liver. The reaction may be conceived as that of phenylalanin being first converted into the corresponding keto-acid (phenyl pyrroacemic) and the latter then into tyrosin by way of oxyphenyl pyrroacemic acid. Tyrosin synthesis from phenylalanin would then be much less extensive in the vitally stained than in the normal liver owing to the strongly diminished oxidative deamination. Phenyl lactic acid is capable of forming aceto-acetic acid in the excised liver, while phenyl pyrroacemic acid does not have this capacity and in fact exercises a disturbing influence on substances so endowed. Now the formation of aceto-acetic acid from phenylalanin in the vitally stained liver might be increased by controlling phenyl pyrroacemic acid formation. Under the influence of carmin staining on tyrosin synthesis from phenylalanin, the liver cells were quite intact and not stained,

while Kupffer's stellate cells showed intense carmin storage and at times strong enlargement. At the end of perfusion the liquid was dealbuminized and the test for tyrosin carried out with naphthalin sulphochlorid melting at 124°. When no soda-carmin solution was employed the dealbuminized perfusion liquid gave a weak Millon's reaction and the substance extracted with ether yielded intense Millon and iron chlorid reactions. With staining, the result was negative. On completion of perfusion the amount of acetone had risen considerably. The amino-acids are probably deaminated hydrolytically in the parenchyma cells, while in so-called histiocytic cells they undergo oxidative deamination.

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**Deamination of the Amino-Acids and Mutual Conversion of the Resulting Products in the Animal Organism.**

*Y. Kotake, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:241, Oct. 6, 1922.*

In the urine of dogs poisoned by phosphorus, l-oxyphenyl lactic acid was detected; this is identical with p-oxymandelic acid, found by Schultzen and Riess in the urine of patients with acute yellow atrophy of the liver. After introduction of l-tyrosin and d,l-tyrosin into the rabbit's organism only the l-form was capable of eliminating oxyphenyl lactic acid, although both forms produced excretion of nearly the same amount of oxyphenyl pyrroacemic acid. From this fact, and bearing in mind the results in vitally stained animals, the amino-acids in the normal animal organism probably undergo, not only oxidative, but also hydrolytic deamination. According to Kiyono the histiocytic cells, particularly reticular endothelium, play an important rôle. The keto-acid, which corresponds to a natural amino-acid and is formed in the organism or is incorporated in it as such, can be converted into the corresponding alcohol acid in the parenchyma cells, probably by an enzyme. This alcohol acid is formed primarily in the organism from a definite amino-acid by hydrolytic deamination or secondarily by the reduction following upon oxidative deamination. It is always optically active and, irrespective of the manner of its formation, it showed rotation in the same direction. Under certain circumstances, also, an alcohol acid can be converted into the corresponding keto-acid. It was shown with certainty that phenyl lactic acid is converted into phenyl pyrroacemic acid. The l-oxyphenyl lactic acid owes its origin chiefly to tyrosin, inasmuch as tyrosin is converted, on the one hand, indirectly by the asymmetric reduction following oxidative deamination and, on the other, directly by hydrolytic deamination, into l-oxyphenyl lactic acid. In this process phenylalanin may also participate by its conversion into l-oxyphenyl lactic acid through phenyl pyrroacemic acid and oxyphenyl pyrroacemic acid.

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**Asymmetric Reduction of Keto-Acids to the Corresponding Alcohol Acids in the Organs.**

*Y. Mori and T. Kanai, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:206, Oct. 6, 1922.*

The keto-acids formed from amino-acids in the body or incorporated in it as such are converted partly into the corresponding optically

active alcohol acids. This conversion depends probably on a reductase in the tissues and such asymmetric reduction should be manifested also by various organs in autolysis. Rotation of the ether-soluble substance prepared from the organic magma could thus be determined in the respective examination of phenyl pyrroacemic acid and oxyphenyl pyrroacemic acid. It is also possible that it might be determined whether asymmetric reduction of this acid by excised dog liver takes place in perfusion experiments under addition of these keto-acids. Both were converted partly into the corresponding levorotatory alcohol acids, l-phenyl lactic acid and l-oxyphenyl lactic acid, in the excised liver as well as in the magma of liver, kidney and spleen.

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**Comparative Researches on the Formation of Aceto-Acetic Acid from d-Phenyl and l-Phenyl Lactic Acid and from d-Oxyphenyl and l-Oxyphenyl Lactic Acid in the Excised Liver.**

*Y. Mori, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:225, Oct. 6, 1922.*

The d,l-oxyphenyl lactic acid was purified completely by recrystallization from water. To 2 gm. of the racemic acid dissolved in 150 c.c. water, 3.4 gm. morphin were added. When the mixture was heated on the water bath, the morphin passed into solution. After the filtered solution stood in the ice-box hard crystals separated; these were suctioned off. The filtrate was concentrated, inoculated with a few of the crystals and kept in the ice-box a few days for further crystallization. Ammonia was added to the 2 united groups of crystals and the liquid filtered. The filtrate was acidified with sulphuric acid, shaken with ether and the ether driven off, whereupon needle-shaped crystals of d-oxyphenyl lactic acid remained. The liver of a dog, which had fasted 24 hours after previous mixed feeding, was rapidly removed after bleeding, the blood defibrinated and mixed with defibrinated blood of another dog, diluted with one-fifth of its volume of Ringer solution and employed for perfusion. Dealbuminization was carried out by Schenk's method, and estimation of aceto-acetic acid according to Huppert and Messinger. Both optically active phenyl lactic acids probably form aceto-acetic acid in the excised liver. Contrary to d-oxyphenyl lactic acid, l-oxyphenyl lactic acid seems to form aceto-acetic acid.

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**Aceto-Acetic Acid from Urocaninic Acid in the Excised Liver.**

*M. Konishi, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:237, Oct. 6, 1922.*

The question arises whether urocaninic acid is a normal intermediate product in the organism. For perfusion experiments on the excised liver by Embden's method, urocaninic acid was obtained from the urine of a dog fed plentifully with histidin and was thoroughly purified by repeated recrystallization. It was found that the liver is able to form aceto-acetic acid from urocaninic acid, though feebly, but to a greater extent than if histidin had been employed alone. This seems to demonstrate that urocaninic acid is a normal intermediate product.

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**Furilalanin. Corrections of a Previous Communication on the Decomposition of Amino-Acids in the Organism.**

*L. Flatow, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 143, Sept. 16, 1922.*

Sasaki and Graenacher doubt the purity of the furilalanin prepared synthetically by the author in 1910 as the submitted nitrogen values are incorrect. At that time 5.29% was given whereas the correct nitrogen content is 9.03%. In the former analysis not furilalanin but its crystallized parent substance, benzoyl furilalanin was dealt with. The constitution of furilalanin was arrived at by rebenzoylation and melting point determination, analysis being dispensed with as the substance, by reason of its toxicity, was of no further interest in relation to the physiologic decomposition of amino-acids in the organism. On its primary production from the saponification products of benzoyl furilalanin the copper salt of furilalanin crystallizes in small, hard, dark blue, irregular crystals in the filtrate, while it is insoluble in pure aqueous solutions.

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**Behavior of Phenylalanin in the Animal Organism.**

*Y. Kotake, Y. Masai and Y. Mori, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 195, Oct. 6, 1922.*

The oxidative deamination of albuminous amino-acids in the animal organism having been demonstrated, the question arose whether phenylalanin undergoes like alterations under the same conditions, the phenyl pyrroacemic acid being excreted in the urine. The d,l-phenylalanin employed for this purpose was prepared according to E. Fischer's directions from benzylmalonic acid over benzyl bromomalonic acid and phenyl bromopropionic acid. Copious administration of phenylalanin produced excretion of phenyl pyrroacemic acid in the urine of rabbits. The phenyl pyrroacemic acid thus formed was converted into oxyphenyl pyrroacemic acid in the organism. Not only l-phenylalanin but also d-phenylalanin and d,l-phenylalanin undergo oxidative deamination in the animal organism. From fourth-day urine extracted with ether a small amount of a substance crystallizing in needles was obtained by treatment with lead acetate and vinegar of lead; this yielded Millon's reaction and its identity with tyrosin was conjectured.

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**The Behavior of Phenyl Lactic Acid in the Animal Organism. I.**

*Y. Kotake and Y. Mori, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 176, Oct. 6, 1922.*

Dogs, rabbits and apes fed with d,l-phenyl lactic acid excreted the d-acid in the urine, while under the same conditions human beings excreted l-acid. There is little probability that in human beings and in these animals the acid is asymmetrically decomposed in such a radically different manner that the former decompose d-acid, the latter l-acid.

The described result is more probably due to predominating decomposition in the human organism of d,l-phenyl lactic acid over phenyl pyrroacemic acid, which is then partly converted in the organism by asymmetric reduction into l-phenyl lactic acid and is excreted in this form. In the animal organism, however, d,l-phenyl lactic acid is split directly, the d-acid remaining intact and being excreted.

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**The Behavior of Phenyl Lactic Acid in the Animal Organism. II.**

*Y. Mori, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 186, Oct. 6, 1922.*

A dog weighing 5.08 kg. received subcutaneous injections of 8 gm. phenyl pyrroacemic acid in the form of sodium salt in 4 portions at intervals of 1½ hours. The urine was collected during 30 hours after the first injection, evaporated on the water bath and then extracted repeatedly with hot alcohol. The alcohol having been driven off the residue was taken up with little water, strongly acidified with sulphuric acid and shaken several times with ether. A little water was added to the ether residue, the mixture warmed and allowed to stand a day; the separated crystals, which were microscopic uniform plates, were suctioned off and dried. Their melting point and properties characterize them as phenyl pyrroacemic acid. The same dog received the same amount dissolved in 500 c.c. cow's milk, orally, within 6 hours. Following the same treatment of the urine only 0.1424 gm. needle-shaped crystals were isolated as against 0.4641 gm. in the first experiment. No phenyl pyrroacemic acid was present. A 19 year old man weighing 58.952 kg. received 10 gm. phenyl pyrroacemic acid in 3 portions at hourly intervals. The urine, collected during 27 hours, contained 1.2434 gm. phenyl pyrroacemic acid after recrystallization from benzene. Here, too, as in the dog, after the filtrate was dried to a syrup, dissolved in ether saturated with sulphurous acid and shaken with saturated sodium bisulphate solution, needle-shaped crystals melting at 124° were obtained from the ether. Thus, the administered phenyl pyrroacemic acid is partly reduced to l-phenyl lactic acid in both organisms.

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**Deamination of Tyrosin in the Animal Organism.**

*Y. Kotake, Z. Matsuoka and M. Okagawa, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 166, Oct. 6, 1922.*

Copious administration of l-tyrosin or d,l-tyrosin in the rabbit is followed by excretion of oxyphenyl pyrroacemic acid in the urine. This shows conclusively that tyrosin undergoes oxidative deamination in the animal organism, at any rate under certain conditions. In this process (particularly when l-tyrosin is given) the animal also excretes a considerable amount of l-oxyphenyl lactic acid which is derived at least partly from the oxyphenyl pyrroacemic acid formed in the organism by asymmetric reduction. The source of the d,l-oxyphenyl lactic acid, small amounts of which were found in the urine in experiments with



l-tyrosin, may perhaps be sought in the intestinal canal, so that the d,l-acid (or possibly the d-acid) there formed from tyrosin is resorbed and excreted as such, or possibly only after its union with the l-acid. That is rendered probable particularly from the fact that in a former experiment on rabbits with l-tyrosin no d,l-oxyphenyl lactic acid but only the pure l-acid was found. Introduced d,l-tyrosin is partly decomposed asymmetrically in the animal organism, d-tyrosin being excreted in the urine in this process. In one of the experiments with d,l-tyrosin abundant excretion of phenol, which had been undoubtedly formed from tyrosin in the intestinal canal, was recognized with certainty.

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**Excretion of Oxyphenyl Lactic Acid under Tyrosin Feeding in Rabbits.**

*Y. Kotake and M. Okagawa, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:201, Oct. 6, 1922.*

A rabbit weighing 2550 gm. received 2 gm. of l-tyrosin 3 times orally at intervals of 3 hours. About every 6 hours the urine was collected with a catheter, each portion being immediately acidified with sulphuric acid and shaken with ether. Collection was maintained for 18 hours until the ether residue no longer yielded Millon's reaction. Urine collected later contained only a small amount of ether-soluble substance giving a very faint Millon reaction. Especially in the first portions, many granular crystals were found. All ether residues received additions of water and the filtered and dried crystals, weighing 0.3023 gm., yielded the iron chlorid reaction, formed hexagonal plates melting at 215° and were undoubtedly oxyphenyl pyrroacemic acid. From the mother liquor, which was concentrated and allowed to stand in the cold, a small amount (about 0.1 gm.) of needle-shaped levorotatory crystals separated, melting at 168°; these yielded Millon's reaction. They were l-oxyphenyl lactic acid. The varyingly repeated experiments showed that administration of even a relatively small amount of tyrosin, independent of its optical property, caused oxyphenyl pyrroacemic acid to appear in the urine, whereas oxyphenyl lactic acid was excreted only as a result of the introduction of a considerable amount of l-tyrosin. The conversion of oxyphenyl lactic acid into oxyphenyl pyrroacemic acid in the animal organism does not take place easily.

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**Formation of Urocaninic Acid from Histidin in the Canine Organism.**

*Y. Kotake and M. Konishi, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:230, Oct. 6, 1922.*

Administration of histidin was expected to show the presence of imidazolyl pyrroacemic acid with imidazolyl lactic acid in the urine. These were not found but urocaninic acid was present. The latter was discovered by Jaffe in the course of feeding experiments with nitro-toluol; Siegfried also found it after injection of sodium tellurate.

Hunter identified it with imidazolyl acrylic acid and Barger and Ewins obtained it synthetically by the action of trimethylamin on  $\alpha$ -chloro- $\beta$ -imidazolyl propionic acid. Raistrick prepared it from histidin by the action of certain microorganisms. Urocaninic acid was always found when a dog was fed liberally with histidin. In the experiment a dog was given 12 gm. histidin monohydrochlorid with 200 gm. beef daily for 2-3 weeks. After working up the urine the acid remained in the form of crystalline prisms with melting point 218-220°. This was insoluble in ether but barely soluble in water and was precipitated by sublimate and silver nitrate. It yielded an intense diazo-reaction and reduced alkaline potassium permanganate solution with formation of  $MnO_2$ . Following subcutaneous injection of histidin monohydrochlorid, urocaninic acid was also found in the urine. This demonstrates conclusively that the conversion of histidin takes place in the tissues.

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**Decomposition of Carbohydrates in Striated Muscle.**

*Fritz Laquer, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:26, Sept. 16, 1922.*

Contrary to the months of February, March and April it is not possible in November, December and January to diminish distinctly the glycogen content of frogs' muscles by maintaining for eight days a temperature of 25-27° C. During the latter months, also, the muscles are not altered by previous heating in such a manner that they form lactic acid from added glucose, after comminution, during 2-4 hours in phosphate solution at 30° C. Under these conditions added glycogen increases lactic acid formation though to a much smaller degree than in the spring or summer months. Glycogen also forms more lactic acid than glucose even when the 2 substances are added to the muscle pulp in concentrations of 5-10%. Injury to the cell structure by repeated freezing in liquid air abolishes almost entirely the muscle pulp's capacity for converting added glucose into lactic acid at 30° C, while the formation of lactic acid from added glycogen is fully maintained. Glucose cannot be decomposed direct from the muscle but only after conversion into a form more capable of reacting and produced directly in the course of glycogen cleavage, in which process a relatively intact cell structure is a prerequisite.

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**Some Observations on Blood Sugar and the Alleged Glycosuria Following Operative Procedures on the Thoracic Duct.**

*Carl S. Williamson, J. Lab. & Clin. Med., 8:19, Oct., 1922.*

Recently observations were made on the blood sugar values and the alleged appearance of glycosuria following a fistula of the thoracic duct or ligation of the duct in the right pleural cavity. The data in the present study have been obtained from experiments on the dog. All operative procedures were carried out under ether anesthesia and with sterile technic. The operative technic for fistula of the thoracic duct was that

of Biedl with Mann's modifications. Following the operation, the ducts were massaged to keep them open. By careful treatment it was possible to maintain a good flow of lymph for from 2 to 3 weeks after the operation.

Before operation, urine was collected and blood was taken for sugar estimations. A second specimen of blood was obtained at the end of the operation, and afterward specimens of urine were taken once or twice daily. Subsequent samples of blood for sugar determination were taken twice daily. All data were carefully recorded during the time the ducts were discharging freely. A fairly wide variation in blood sugar values was found. The occasional postoperative increases were not sufficient to be significant. The average postoperative blood sugar value, disregarding the reading obtained immediately after operation, is practically the same as that immediately prior to operation. With regard to sugar in the urine findings were uniformly negative before and after operation. Apparently the importance of the lymph stream as a potential carrier of the pancreatic secretion has been overestimated.

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### **The Effects of Insulin on Experimental Hyperglycemia in Rabbits.**

*F. G. Banting, C. H. Best, J. B. Collip, J. J. R. Macleod and E. C. Noble, Am. J. Physiol., 62: 559, Nov. 1, 1922.*

The authors have previously shown that a marked fall occurs in the percentage of blood sugar in normal rabbits when they are injected subcutaneously with insulin. The latter also reduced, often to the normal level or below it, the high percentages of sugar found in the blood of depancreatized dogs and of diabetic patients. This investigation was undertaken to obtain further evidence as to the action of insulin by studying its effect on the various experimental conditions that are known to cause marked hyperglycemia in rabbits. Rabbits of uniform size and breed were fed with an abundance of oats and hay, sometimes with sugar added, for some days preceding the experiments. The blood was collected at frequent intervals in 1 c.c. quantities from the ear veins and the percentage of sugar determined by the Schaffer-Hartman method. At the termination of the experiments, whenever possible, the percentage of glycogen in the liver was estimated by Pflüger's method, using the Schaffer-Hartman method for measuring the reducing power of the hydrolyzed solutions. The insulin used was not always of uniform potency, so as a preliminary to each experiment the preparation of insulin was injected into normal rabbits. If the insulin was found to be active, either the same rabbit or another normal rabbit was subjected to one or more of the following procedures for the production of hyperglycemia: piqûre, injection of epinephrin, mechanical asphyxia, carbon monoxid poisoning and ether. The authors found that these factors do not cause the usual degree of hyperglycemia when the fall in blood sugar due to subcutaneous injection of insulin is thoroughly established. Even when the insulin is given at the same time that the animal is subjected to the experimental condition used to cause hyperglycemia, the latter may be either entirely absent or greatly diminished.

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**The Output of Sugar from the Liver as Affected by  $C_H$  and Minimal Epinephrin.**

*C. D. Snyder, L. E. Martin and M. Levin, Am. J. Physiol., 62:442, Nov. 1, 1922.*

The reverse action of minimal amounts of epinephrin has already been demonstrated for the portal-venous system of the terrapin's liver by Snyder and Martin. The present work was undertaken to determine how the output of sugar by the liver under similar conditions is affected. The terrapin's liver was used and the method of perfusing it identical with that described by Snyder and Martin. Ringer's solution buffered with phosphates was used and in some of the experiments a small amount of dextrose was added. Four reservoirs contained the solutions, 2 of which were set at lower and 2 at higher pH; to 1 of each of these pairs adrenalin-Takamine was added in the ratio of 1:10. The outflow from the hepatic veins was collected in 50 c.c. graduated flasks and the time required for filling to scratch mark observed on a stop-watch, thus permitting the outflow to be reduced in all cases to definite time periods for comparison. The livers were perfused for some time before samples were taken. The analysis of the samples consisted of (1) removal of protein; (2) filtering; (3) concentrating on the water-bath, exact original volumes always being noted to which the sugar content was finally referred; and (4) analysis for reducing substances.

The tabulated results show that the volume outflow per unit of time in general is greater for the solution of lower pH, less for the solution of higher pH. The output of reducing substances per unit of time in the venous outflow is greater for the solution of lower pH, less for the solution of higher pH. The mean difference of 5 of the authors' observations was as much as 78%. When minimal effective amounts of adrenalin-Takamine are added to the perfusing fluids of low and high pH indices, the minute-volume outflow for solutions of higher pH is markedly less and for solutions of lower pH markedly greater, than for adrenalin-free solutions of equal pH values. The minute-weight output of reducing substances for solutions of higher pH is markedly less, and for solutions of lower pH markedly greater, than for adrenalin-free solutions of equal pH values. The authors conclude that the great variations in output of reducing substances produced by minimal amounts of adrenalin are to be ascribed more to the direct effects of the drug on vascular caliber and hence upon intensities of irrigation, than directly upon the glycogenolytic processes of the liver, even though the data presented above would appear to point to a specific epinephrin reversal for the process of hepatic glycogenolysis.

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**Reproduction on Synthetic Diets When Purified Agar is Added to the Mixture.**

*Helen S. Mitchell, Am. J. Physiol., 62:557, Nov. 1, 1922.*

Mitchell observed that rats on a synthetic diet consisting of starch, salt mixture, butter fat, crisco, and dry yeast as a source of vitamin B, grew to a large size and were apparently in splendid condition, but frequently failed to breed. Believing that bulk might be a beneficial

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factor, 2 female rats which had been on the standard casein diet for 14 and 25 weeks respectively, and had been mated without result, were again mated with the same male after agar had been added to the food and the following month produced and raised litters of 7 and 10 respectively. Since the agar used in these experiments was a highly purified product containing only slight traces of salts which were already present in the food in abundance, this factor cannot be held responsible for securing reproduction. The author believes the observations described point to the importance of roughage, as such, in the diet of the rat.

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**Studies in Inorganic Metabolism. I. Interrelations between Calcium and Magnesium Metabolism.**

*L. Jean Bogert and Elizabeth J. McKittrick, J. Biol. Chem., 54: 363, Oct., 1922.*

This experiment was undertaken to ascertain whether an increased intake of calcium would affect the urinary and fecal excretion of magnesium and vice versa, thus showing interrelations between the metabolism of these two elements. Four healthy young women lived for 16 days on an absolutely uniform experimental diet which furnished 0.266 gm. calcium and 0.275 gm. magnesium per day for subjects A and B, and 0.309 gm. calcium and 0.292 gm. magnesium for subjects C and D. A calcium-low diet was given for 4 days prior to the beginning of the experiment proper, and also at the close of the experiment until the last collection of feces was made. The experimental period proper was divided into 4 periods of 4 days each. Period 1 represented normal calcium and magnesium intake. Period 2, magnesium-high and calcium-normal intake, the magnesium being raised by adding to the regular diet 6 gm. magnesium citrate in 3 equal doses daily. Period 3 was exactly like Period 1. Period 4 represented calcium-high and magnesium-normal intake, the calcium being raised by adding to the diet 6 gm. calcium lactate in 3 equal doses daily. The experimental periods were marked off in the feces by the taking of carmin just before the first meal of each period. The tabulated data resulting from the experiments show that the addition of 6 gm. magnesium citrate per day to the experimental diet increased urinary and fecal magnesium in all 4 cases. The added magnesium also increased the urinary and fecal calcium in 3 out of 4 cases, and the total calcium excretion in all 4 cases. The addition of 6 gm. calcium lactate per day to the experimental diet led to decided increases in both urinary and fecal calcium in all 4 cases. No definite conclusions as to the influence of the calcium lactate upon magnesium metabolism were reached.

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**Studies in Inorganic Metabolism. II. The Effects of Acid-Forming and Base-Forming Diets upon Calcium Metabolism.**

*L. Jean Bogert and Elizabeth E. Kirkpatrick, J. Biol. Chem., 54: 375, Oct., 1922.*

The diets in these experiments were planned to yield uniform amounts of energy, protein, calcium and fat throughout the experi-



mental period which was divided into 4 periods of 4 days each. A 4 day period of calcium-low diet preceded the experiment. The same calcium-low diet was taken in the after-period until the last marker appeared in the feces. In the first and third periods, diets were selected so that the excess of base furnished by certain foods was practically balanced by the excess of acid supplied by other foods. The diet of the second period consisted almost entirely of base-forming foods, and that of the fourth, of acid-forming foods. The data for the acidity or alkalinity of the foods were taken from Sherman's tables, which express the excess of acid or base in cubic centimeters of normal solution. The balanced diet consisted of beef, peanut butter, bread, rice, potatoes, milk, apples, butter fat, and sugar; the base diet, of apples, milk, peas, potatoes, peanut butter and sugar; and the acid diet of bread, rice, eggs, milk, butter fat, and sugar. The authors' tabulated data show that the base-forming diets consumed in Period 2 resulted, in every case, in a decided diminution in urinary calcium, while the acid-forming diets of Period 4 caused a marked increase in urinary calcium in 3 out of 4 subjects. There was a tendency of the base-forming diets to divert calcium from the urine to the feces, and of the acid-forming diets to increase urinary calcium at the expense of fecal calcium. Of the 4 subjects, 3 showed a noticeable increase in total calcium excretion and 2 showed increased negative calcium balances, not to be accounted for by calcium deficiency in the diets, during the period in which the acid-forming diets were consumed. The total calcium excretion during the period of the base-forming diet was lower than in the preceding period in 3 subjects and about the same in the fourth. These results tend to indicate that calcium is retained somewhat more readily on a basic diet than on balanced or acid-forming diets, while calcium excretion is greater on an acid-forming diet than on balanced or base-forming diets.

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**Studies in Inorganic Metabolism. III. The Influence of Yeast and Butter Fat upon Calcium Assimilation.**

*L. Jean Bogert and Ruth K. Trail, J. Biol. Chem., 54:387, Oct., 1922.*

These experiments deal with the possible relation between the vitamin content of the diet and calcium excretion in normal women. Experimental time was divided into 4 periods of 4 days each, with fore and after periods on calcium-low diet. Diets of first and third periods were the same—lean beef, rice, skimmed milk, white bread, sugar, corn-starch, and purified fat from nut margarin—very low in vitamins. In the second period, yeast was added to supply vitamin B; in the fourth period an equal weight of butter fat was substituted for the vegetable fat to give vitamin A. The diets were planned to meet the energy, protein, and calcium requirements of the subjects. The tabulated results show that the addition of yeast to a basal diet, practically free from vitamins, led to lowered excretion of calcium in normal women. The substitution of an equal weight of purified butter fat for purified fat from nut margarin in the vitamin-free diet also resulted in decreased calcium elimination. It appears then that the vitamin content of the diet exerts some influence upon calcium assimilation.

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**The Rôle of the Vitamins in Cell Chemism.**

*Emil Abderhalden, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:88, Sept. 16, 1922.*

These remarks were called forth by an article by Hess (SURVEY, April, 1922, 1a-243). According to Abderhalden the phenomena of alimentary dystrophy are related to the diminished oxidizing capacity of the cells. Hess conceives that he was the first to furnish the experimental proof. Abderhalden, utilizing the influence on respiration as indicator, endeavors to determine this or the active substances, whereas Hess's procedure embraces experimental analysis and elucidation of the special character of respiratory insufficiency. In Abderhalden's view cellular gaseous exchange is disturbed in alimentary dystrophy in pigeons. It can be increased by addition of some unknown substances from yeast or bran. The exact nature of this disturbance is still obscure. In alimentary dystrophy diminished cell respiration can always be increased by definite products, such as bran extracts, while the respiratory activity of cells under the influence of hydrocyanic acid is not affected. In animals fed on rice convulsions can be induced by diminishing the oxygen content of inspired air or by increasing the carbon dioxid content.

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**The Vitamin Problem. I. Gaseous Metabolism in White Mice on Avitaminous Feedings.**

*Franz Groebbels, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:104, Sept. 16, 1922.*

In white mice fed on polished rice, which showed no abnormal behavior excepting debility and respiratory alteration that set in shortly before death, there were 2 typical metabolic changes, viz. increase and then a continual decrease in oxygen consumption and body weight. The initial increase in metabolism, less prolonged in young than in older animals and found also in human beings affected by avitaminosis, represents a general avitaminosis. The decrease in oxygen consumption and body weight after the initial increase is regarded as the effect of secondary injury to the general protein and salt metabolism and is therefore not a direct expression of avitaminosis. Addition of aqueous thymus extract to the diet in 2 cases showed absence of increased metabolism with barely prolonged duration of life. In the debility stage avitaminous white mice can be resuscitated by pure oxygen and their life prolonged. Following exhaustion of the vitamin reserves in the body the injury to general cellular protein and salt metabolism differs only in degree and not in kind from an inanition effect. Diminution of metabolism and of tissue respiration is present in all animals in a late stage of avitaminosis and is conditioned by a relative hunger effect upon the cell.

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**The Synthesis of Water-Soluble B by Yeast Grown in Solutions of Purified Nutrients.**

*Margaret B. MacDonald, J. Biol. Chem., 54:243, Oct., 1922.*

MacDonald and McCollum have shown that yeast can be grown in a solution of purified nutrients in quantities sufficient for feeding.

The object of the experiments herein recorded was to determine, through feeding tests with young rats, whether such yeast would serve, as do baker's and brewer's yeasts, as a source of water-soluble B. Positive results would indicate the synthesis of the vitamin by the yeast cell. With this object in view 3 varieties of yeast were grown in Nutrient Solution 1 (previously described by MacDonald and McCollum) and dried at room temperature. From 0.1 to 0.4 gm. of this yeast was administered daily to young rats that had been kept on a diet free from water-soluble B until they began to lose weight. The results were unsatisfactory so a second test was made in which the yeast grown in a sterile solution of mineral salts, ammonium sulphate, and cane sugar, formed 2% of the diet of young rats after a period of water-soluble B-free diet. This test also proved unsatisfactory so a third test was made in which several varieties of yeast grown under definite conditions formed a higher percentage of the diet of young rats. Cultures of *Saccharomyces cerevisiae* and *Saccharomyces ellipsoideus* were obtained from Parke, Davis and Co.; cultures of yeasts XII and K were furnished by the Fleischmann Laboratories and 1 culture was plated from a commercial yeast but not identified. These 5 varieties of yeast were carried through 10-20 successive seedings in Nutrient Solution 3, which contained 1 liter of distilled water; 50 gm. cane sugar; 2 gm. potassium dihydrogen phosphate, c.p.; 2.35 gm. ammonium sulphate, c.p.; 0.25 gm. calcium chlorid, c.p.; 0.25 gm. magnesium sulphate, c.p.

Young rats, weighing 60-70 gm., were placed on a basal diet adequate for growth in every respect excepting that it lacked water-soluble B, until they began to decline in weight. This constituted Period 1 in the growth charts given in the article. During Period 2, 5% of yeast replaced that amount of dextrin in the basal diet. In compounding the ration air-dry yeast was ground in a mortar and thoroughly mixed with the other ingredients. Another chart shows the growth curve of a control rat that was kept on the basal diet until quite feeble. During Period 2 it received a ration in which 4% of wheat embryo replaced that amount of dextrin in the basal diet. From a study of the growth curves given in the article, those of the rats receiving yeast grown in Nutrient Solution 3 do not differ markedly from those of rats receiving yeast from other nutrient solutions. The author remarks that, in as far as its content of water-soluble B is concerned, yeast grown in solutions of purified nutrients is much like yeast grown in other mediums.

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**Yeast as a Source of Vitamin B for the Growth of Rats.**

*Cornelia Kennedy and Leroy S. Palmer, J. Biol. Chem., 54:217, Oct., 1922.*

The authors wished to determine the lowest level at which yeast could be fed to growing rats and still produce results which were as satisfactory as those given by the use of the alcoholic extract of ether-extracted wheat embryo. Groups of rats in colonies were fed on a basal ration of purified casein 18%, salts 3.7%, agar 2%, butter fat 5%, with dextrin to make 100%. Vitamin B was supplied in the form of

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dried yeast of various sources, both as an integral part of the ration or separately in the form of a tablet, the latter procedure being found satisfactory. In reporting their results the authors have taken into consideration the amount of nitrogen added to the ration by the yeast and also the actual weight of pure yeast that was necessary to add to obtain growth. The tabulated data and growth curves presented do not support the general belief that yeast is an unusually valuable source of the growth-promoting vitamin B, or that it can be accepted as a standard product in experiments in which a vitamin B preparation is required. The failure of the rats to reproduce normally and rear their young is considered one of the strongest arguments against the use of yeast as a source of vitamin B. Another objection is that the amount of unknown material added to an otherwise carefully purified ration is greater and of a more complex nature when yeast is added than when an alcoholic extract of yeast or some other vitamin-containing foodstuff is employed.

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**Studies on Vitamins B and D.**

*Casimir Funk and Julia B. Paton, J. Metab. Research, 1:737, June, 1922.*

In 1913 Funk suggested the probability of vitamin B playing a rôle in carbohydrate metabolism. In view of criticisms of this premise, the experiments were repeated in a different way, noting (1) the rôle of vitamin B in metabolism, (2) the influence of carbohydrate and proteins on pigeons' vitamin B requirements, (3) variations in individual pigeons' vitamin B requirements, (4) storage of vitamin B, (5) action of alkali, high temperature and atmospheric contamination on vitamins B and D, (6) influence of yeast growth on vitamins B and D. Pigeons were considered more suitable than rats for testing vitamin B because of the complicated vitamin requirements of rats. A shortened procedure for testing vitamin B on pigeons is described in which each bird is kept in a separate cage with control of food intake and daily weighing, whereby the completeness of chemical fractionation can be determined in 4 or 5 days.

Further evidence is presented on the vitamin-sparing action of certain proteins free from vitamin B. Results showed that increasing carbohydrate did not give clear indications of increased vitamin requirement and that increasing the amount of vitamin B did not increase the intake of a well-balanced diet. Individual pigeons show great variations in vitamin B requirements, which is of the greatest importance in testing this vitamin in pigeons. Alkali is markedly destructive to vitamin B, less to vitamin D. Autoclaving for 3 hours at 25 lb. pressure is destructive to vitamin B, less so to vitamin D. Experiments on the effect of alkali and autoclaving on pigeons already in vitamin B equilibrium are the first of their kind. Contrary to prevailing views, and to the authors' surprise, growth of yeast or some other fungus takes vitamin D out of solutions and leaves vitamin B behind, as shown by experiments on pigeons and rats. The yeast cells retain the D vitamin tenaciously. This biologic method of separation is applicable to the elimination of vitamin D from a mixture of

vitamins B and D. A series of charts, tables and illustrations record and elucidate experimental procedure and results.

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**The Growth-Promoting Factor in Lemon Juice. I. In What Way is Its Effect on Bacteria Influenced by Physical, Chemical and Colloidochemical Methods?**

*Bruno Leichtentritt and Margarete Zielaskowski, Biochem. Ztschr., Berlin, 131:499, Sept. 16, 1922.*

Attempts were made to utilize the accessory nutritive factors as described by Hopkins and Hofmeister in the field of bacteriology. A staphylococcus strain from osteomyelitis pus was cultivated on agar plus lemon juice or extract of carrot obtained by autolysis. This was a strain which did not thrive on the ordinary nutritive mediums, agar, blood, serum and ascites plates. In attempts at overcoming, by physical, chemical and colloidochemical methods, the action of the lemon juice in furthering the growth of bacteria, it was found that lemon juice treated in the autoclave did not lose any of its growth-furthering action. In hydrolysis with hydrochloric acid in the autoclave the same result was obtained, while by hydrolysis with lye there was a slight weakening of the action. Hydrolysis with 2-3% hydrochloric acid generally does not injure the growth-furthering action, in contrast with that with sodium hydroxid. Independently of the reaction, whether acid or alkali, the growth-furthering characteristic of lemon juice is not inhibited by irradiation with ultraviolet light, no matter whether it is heated at the same time or not. Nor do Roentgen rays inhibit this action. If  $O_2$  is passed through acid lemon juice and it is alkalized afterward, this does not have the slightest effect on the bacterial growth. The same negative result is obtained by boiling acid or alkalized lemon juice and at the same time passing  $O_2$  through it. Here there is an undoubted difference between the procedure of boiling and of aëration in the antiscorbutic factor in animal experiments and in bacterial growth. If acid lemon juice is left 4 days in an open dish in the incubator its action in furthering bacterial growth is not injured. By treating lemon juice with adsorbents, kaolin, charcoal and talcum, its growth-furthering action could be weakened if not completely destroyed. The preliminary treatment of the lemon juice is irrelevant. The greater part of the substance which furthers bacterial growth is dialyzed, independently of the acid reaction. The rind content is considerably weakened.

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**The Growth-Promoting Factor in Lemon Juice. II. Comparison between Guinea-Pig and Bacterial Plate Experiments.**

*Bruno Leichtentritt and Margarete Zielaskowski, Biochem. Ztschr., Berlin, 131:513, Sept. 16, 1922.*

The results obtained on agar plates in reference to the influence of physical, chemical and colloidochemical methods on the growth-promoting influence of lemon juice on bacteria were retested in guinea-pig experiments. The guinea-pig is sensitive to scurvy. If the



results of animal experiments harmonize with those of plate experiments, the latter method could be used for testing antiscorbutic substances. Guinea-pigs were fed with oats and 4 gm. dry milk and kept under the necessary conditions for metabolism experiments. It was found that guinea-pigs which received lemon juice that had been heated twice for an hour in the autoclave were protected against scurvy for a long time, over twice as long as the control animals receiving no lemon juice. But the final onset of the disease could not be prevented. All other changes in the constitution of the lemon juice had a harmful effect on the guinea-pigs and caused scurvy, the only difference being in the quantitative injury. Any change in the structure of lemon juice by heat, as well as by irradiation with ultraviolet light, injures its antiscorbutic efficiency very little. On the other hand, by simply standing at room temperature the lemon juice is denaturized. This process of aging causes much greater injury to the antiscorbutic properties of lemon juice than does, for example, heating under pressure with the addition of mineral acids. Antiscorbutic factor C shows considerable variations in animal experiments, all of the animals becoming scorbutic with the exception of those that received lemon juice which had been subjected to ultraviolet light or aëration. Adsorption experiments disclosed that the factor which promotes bacterial growth is only partly absorbed, in contrast with the antiscorbutic factor. It may therefore be assumed that lemon juice contains several ferments, the different actions of which indicate the presence of (1) antiscorbutic factor C and (2) a growth-promoting factor that is effective on children who are not thriving (with Barlow's disease) and on certain kinds of bacteria. The latter factor might properly be termed vitamin D, as Funk has suggested.

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### **Faulty Diet and Its Relation to the Structure of Bone.**

*P. G. Shipley, J. A. M. A., 79: 1563, Nov. 4, 1922.*

The author's study of the growth and physiology of bone revealed that several dietetic principles are concerned in the growth of bone: (1) an uncharacterized organic substance which is distinct from fat-soluble vitamin A; (2) calcium; (3) phosphorus; and (4) water-soluble vitamin B and fat-soluble A. Bones of animals whose diet is adequate except for fat-soluble A are perfectly calcified, but a high degree of osteoporosis develops. The same result follows the administration of diets having a deficiency only in water-soluble B, but the latter deficiency produces also an aplasia of the marrow and hemorrhage into the medullary cavity. If a guinea-pig is deprived of water-soluble C, the bones are identical with those of a rat which has been given an insufficient supply of water-soluble B. If the organic substance referred to above (which is abundantly present in fish oils) is supplied to animals freely, rickets will not develop in spite of a faulty ratio of calcium to phosphorus in the diet. Animals are able to compensate for faulty calcium-phosphorus ratios in the diet if they are exposed to the rays of the sun or iron-chromium or cadmium arcs or to mercury vapor quartz light.

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**Studies on Experimental Rickets. XXIII. The Production of Rickets in the Rat by Diets Consisting Essentially of Purified Food Substances.**

*E. V. McCollum, Nina Simmonds and J. Ernestine Becker, J. Biol. Chem., 54:249, Oct., 1922.*

The experiments herein recorded were carried out under hygienic conditions in respect to temperature, cleanliness, ventilation and opportunity for exercise. Direct sunlight was eliminated. Diets employed were: (1) Wheat germ (extracted with ether and chloroform), wheat gluten (purified), gelatin, agar-agar, salt mixture XXI,  $\text{CaCO}_3$ , purified dextrin,  $\text{NaH}_2\text{PO}_4 + \text{H}_2\text{O}$ , and butter fat. (2) Wheat germ (extracted with ether and chloroform), wheat gluten (purified), gelatin, purified casein, agar-agar, salt mixture XXI,  $\text{CaCO}_3$ , purified dextrin and butter fat. Salt mixture XXI contains  $\text{CaCO}_3$ ,  $\text{KCl}$ ,  $\text{NaCl}$ ,  $\text{NaHCO}_3$ , and  $\text{FeSO}_4 + 7\text{H}_2\text{O}$ . The rats on these diets showed marked signs of rickets at autopsy, and on histologic examination all the characteristic features of the disease were found in the bones. In addition the animals developed xerophthalmia, notwithstanding the presence of sufficient fat-soluble A to cover the minimum nutritive needs.

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**Experimental Rickets in Rats. IX. The Distribution of Phosphorus and Calcium between the Skeleton and Soft Parts of Rats on Rachitic and Nonrachitic Diets.**

*Gertrude F. McCann and Marion Barnett, J. Biol. Chem., 54:203, Oct., 1922.*

The authors wished to determine what occurred when rats were given diets that were extremely poor in phosphorus or in calcium: whether the bones and soft tissues shared the amount proportionally, or whether a point could be reached at which one or the other would suffer the greater deprivation. The protection afforded these rats when exposed to sunlight or when receiving cod-liver oil was also noted in an effort to determine if the mode of protection was by a greater absorption and retention of phosphorus by the entire body or a redistribution of it so that the bones could retain a larger share.

White rats were given various experimental diets for about 30 days when roentgenograms were made and the rats killed by etherization. The entire gastro-intestinal tract was removed and discarded. A piece of one middle rib was removed for histologic examination. The bones and the soft parts were separately ashed and the phosphorus determined by titration of ammonium phosphomolybdate, while the calcium was determined by McCrudden's method gravimetrically. The authors' tabulated results show that rachitic rats contain less phosphorus and calcium per 100 gm. body weight than do normal rats. This is most marked where the greatest growth has occurred. This reduction is the same whether the rickets was produced by a diet poor in phosphorus and rich in calcium or by one poor in calcium and rich in phosphorus. In rachitic rats, the bones may contain a smaller percentage of the total phosphorus than is found in normal rats. This

difference is not marked except where fair growth has occurred. When rickets is prevented from developing in rats given a diet poor in phosphorus but rich in calcium, by administration of cod-liver oil or by exposure to light, the total phosphorus and calcium content per 100 gm. body weight is well within the normal range.

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**The Effect of Defective Diets on Teeth. The Relations of Calcium Phosphorus and Organic Factors to Caries-Like and Attaching-Tissue Defects.**

*Clarence J. Grieves, J. A. M. A., 79:1567, Nov. 4, 1922.*

In the author's experiments 85 rats, about equally divided as to sex, were placed in groups on the following diets: (1) low calcium diets; (2) low calcium and low fat-soluble A diets; and (3) high calcium and high butter-fat diets. Percentages of lesions ensuing were calculated on the number of teeth involved (12 molars); the number of rats placed on these diets, and the period on the diet which averaged 120 days. In Group 1, 22% of the rats showed caries-like defects and 3.65% of their molars were involved. Attaching-tissue-lesions were manifested by 41% of the rats, the molars being involved to the extent of 57.9%. In Group 2, 31% of the rats showed caries-like defects and 5.21% of their molars were involved. Attaching-tissue defects were manifested by 20%, the molars being involved to the extent of 17.7%. In Group 3, 17% of the rats showed caries-like defects involving 1.73% of their molars while attaching-tissue defects, affecting 33% of the molar attachments, were manifested by 28% of the rats.

The essentials of dental caries, according to the modern conception, are environmental. It is believed that caries progressively invades teeth from without inward and may result from chemicomicroorganic causes in any retention center. Whatever the bacterial types, they are presupposed to produce sufficient acidity to decalcify enamel and dentin, and to be sufficiently proteolytic to complete dentinal destruction. Such a conception does not exclude the possibility that teeth may not be predisposed to caries from developmental structural defects, which may result in early formative periods and may assist in localizing carious lesions. The attaching-tissue defects reported occurred in 2 groups: (1) the atrophic types, with progressive horizontal and regular loss of alveolar crests, the cortex remaining hard, rounded and smooth; and (2) the infective type, with irregular vertical invasion of the alveolar walls and localized root exposure, in which the cortex is rough, porous or missing, as in true pyorrhea.

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**Decalcification of Teeth and Bones and Regeneration of Bone through Diet.**

*Percy R. Howe, J. A. M. A., 79:1565, Nov. 4, 1922.*

Many observers have reported the similarity of teeth and bone as regards chemical composition, inorganic constituents, density of cartilage and process of calcification. It seems reasonable to infer, then,

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that a pathologic condition which affects one may affect the other. Concerning dental caries, however, the general opinion of dentists has been that this condition is brought about by local fermentation of carbohydrate with the formation of lactic acid, producing eventually a cavity of the tooth. The author presents experimental evidence to show that a metabolic factor may be partly responsible for the production of dental caries. When guinea-pigs were fed for a long time on a scorbutic diet, extensive decalcification of teeth and of some parts of the bones followed. Calcification occurred when the animals were subsequently placed on an antiscorbutic diet. The author doubts whether in all cases the recalcification was wholly due to the diet. It may be that in some cases tissue degeneration proceeded to the point of calcification.

## RESPIRATORY SYSTEM

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### Respiratory Epithelium and Respiration.

*Alfred Plant, Deutsch. Arch. f. klin. Med., Leipsic, 140:129, Sept. 5, 1922.*

The neglect of the alveolar epithelium is not due to the idea that the epithelium does not have any function in the glandlike structure of the lung; recent investigations have attempted to show that the alveolar epithelium as active cells secrete the respiratory gases. Habituation to high altitudes is said to take place primarily through a secretory function of the alveolar epithelium, which is such an infinitely fine structure that it is almost never seen. In man as in mammals it consists in postnatal life of 2 structures, the mononuclear basal cubical cells and large, thin, nonnucleated and structureless pavement cells. If according to the secretory theory the epithelium of the lung had an active part in external respiration, this function would have to be carried on by the cells which have nuclei. According to histologic findings, however, it is the nonnucleated pavement cells which are contiguous to the lung capillaries and have to do with gas exchange; the nuclear cells lie in the spaces between the vessels and are little or not at all concerned in the passage of oxygen and carbon dioxide. According to the diffusion theory the nonnucleated pavement cells are excellently adapted for this purpose if the gases simply pass through the layers between the blood and the alveolar air. In that case the layers cannot be thin enough; the nucleus and granules not only take up space and offer resistance but by adsorption and absorption of gas decrease the respiratory effect.

Corresponding to the phylogenetically gradual development of the lung, it may be assumed that there are transition forms. In the amphibia (frogs) where the need of oxygen is only supplied in part by pulmonary respiration, all the alveolar epithelial cells have nuclei. The nucleated cells, whose protoplasm is also granulated, always lie in the capillary meshes, but over the capillaries themselves lies very thin structureless protoplasm. If the delicacy of the alveolar epithelium is proportional to the functional capacity of the lungs, then an extraordinarily thin layer of epithelium would be expected in the lungs of birds, which perform a much heavier task than those of man or mammals. The histologic and functional character of the anatomic

substrate of respiration seems especially clear in the more primitive respiratory organs. These show in their incompleteness a striving toward the condition that exists in the finished lung, of enlargement of capillary surface and decrease of tissue resistance between the external air and the capillary blood.

The attempt to create a respiratory surface suited to breathing air and protected against drying, which must, therefore, lie inside the body was attempted in several places in the digestive tract. This was impossible where, as in the mouth and esophagus, stratified epithelium prevented the necessary thinning of the epithelium, and farther down the opposition between intestinal and respiratory function was too great to enable a good permanent respiratory organ to be produced. It was reserved for the extroversion of the intestinal tube-lung to become a respiratory organ capable of development. A respiratory organ is a stranger in the digestive system and gives rise to disturbances. As respiratory epithelium developed from the flattening out and structural simplification of higher and more complex epithelial cells, so on the other hand high cylindric cells with complex protoplasmic structure, which are derived from simple basal epithelium, are true gas gland cells. These offer the sharpest sort of contrast to the flat, nonnucleated, homogeneous alveolar epithelium cells. Gas secretion in the lungs is not compatible with the histologic picture. In respiration there is a simple diffusion of oxygen and carbon dioxid through the epithelium of the respiratory organs.

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**Physiologic and Pharmacologic Studies on Respiration in Cold-Blooded Animals.**

*F. Felix Werner, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196: 83, Sept. 27, 1922.*

In the respiration of the frog 2 different forms of laryngeal movement are observable, namely superficial movements alternating with deeper elevations and depressions of the floor of the mouth. To permit more exact analysis the movements were recorded by means of mirrors with Frank's kymograph. A lever provided with a mirror fastened in the region of the submaxillary muscle by a fine German silver wire registered the respiratory movements. A specially constructed double lever served for simultaneous registration of respiratory and cardiac movements. Of substances causing primary injury to the respiration center there were examined urethan (0.0037 gm. per gram of frog) and chloral hydrate (0.003 gm. per gram of frog), of those producing secondary injury the digitalis substances (strophanthin) and also poisons causing spasms (strychnin). Stimulation of the normal respiration center was carried out with injections of atropin-sulphuric acid ester. These various drugs abolish coördination of the respiratory movements. As shown by photographic registration urethan stops the expiratory and inspiratory phases while epiglottic oscillations are preserved, whereas chloral hydrate abolishes the oscillations but does not affect expiratory and inspiratory phases. This stage is designated intermittent apnea by the author. The secondary injury to respiration by strophanthin coincides, as a rule, with the first ventricular tonus increase. The strychnin effect will be analyzed more closely in another

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research. Tetanus is induced by forced expiration (shriek) with collapsed lungs. If the stimuli follow at moderate intervals this cannot be utilized by the animal for oscillation. On the contrary there is an endeavor to fill the lungs fully by means of the greatest possible number of inspirations. Atropin-sulphuric acid ester has a stimulating action on the normal respiration center and on that injured by choral hydrate.

## NEUROMUSCULAR SYSTEM

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### **The Refractory Phase in a Reflex Arc.**

*E. D. Adrian and J. M. D. Olmsted, J. Physiol., London, 56: 426, Oct. 18, 1922.*

The authors determined the maximum frequency of response in the cat's tibialis anticus muscle to reflex and motor nerve stimulation and compared this with the least interval for muscular summation in the same animal. In the arc for the flexion reflex in the spinal cat they found that the least interval which must separate 2 stimuli giving a summated contraction to be about 0.0019 second when the stimuli are applied to the afferent nerve and 0.0017 second when they are applied to the efferent nerve. When conduction in the central part of the arc is abolished by an anesthetic the interval for reflex muscular summation remains constant until conduction fails. Thus the second impulse, which arrives at the anesthetized region 0.006 second after the first, has no greater difficulty in passing through than had the first impulse. The region on which the anesthetic takes effect (the synaptic region) has therefore recovered its normal conductivity within 0.006 second of the passage of an impulse. This is a shorter time than in the motor nerve, which recovers normal conductivity in 0.01 second.

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### **A Simple Technic for the Preparation of a Spinal (Headless) Animal.**

*Reginald Alex Cutting, J. Lab & Clin. Med., 8: 44, Oct., 1922.*

This method, devised by the author, has proved simple and serviceable. The animal (cat, dog, rabbit, etc.) should be preferably a male in good physical condition. Ether anesthesia is induced in the usual manner and is maintained with the ether bottle after tracheotomy. The incision for the latter should extend from the lower margin of the cricoid cartilage nearly to the suprasternal notch. Starting from the laryngeal end of this incision, 2 secondary skin incisions are carried upward and backward to encircle the neck and meet dorsally in the median line at the level of the atlantoöccipital articulation. The cervical margin of the skin, including the deep fascia, is now dissected up and turned back for several centimeters, thus exposing the musculature of the neck. The closed blunt points of long curved hemostatic forceps are next plunged under the anterior musculature at the level of the third cervical vertebra, entering them just behind the external jugular vein on the left, working through just anterior to the vertebral column, and bringing them out on the right side, also just posterior to

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the external jugular vein; the end of a strong waxed cord is now caught between the jaws of the forceps, and the latter is withdrawn, thus pulling the cord through the musculature. The cord is tied tightly about the muscle mass without including the trachea; this maneuver shuts off the blood supply through the 2 carotids and the external and internal jugular veins. The hemostats are inserted as before at the same point, but this time they are worked through the musculature posterior to the vertebral column and are brought out in the median line at the level of the third cervical vertebra; a ligature is passed and tied as previously described. The corresponding muscle group on the right side is also tied off. At this point 5 c.c. of a 1:10,000 solution of adrenalin in normal saline is injected subcutaneously in the flank, the ether supply is cut off, artificial respiration introduced, and heat is supplied to the body by means of an electric pad, a bank of incandescent electric lights, or the like. The vertebrae are now occluded, by successively inserting the hemostats beneath each of the muscle groups already tied, drawing the cord so as to encircle the spinal column, tying the ligature tightly and working it down firmly between the second and third cervical vertebrae. At the end of 5 minutes, if the heart still continues to beat properly, the head is severed from the body above the ligatures, the incision being carried through the vertebral column between the atlas and the occiput. The blood pressure rises slowly; reflexes may be expected to return gradually at the end of 20 minutes.

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**A Study of the Action Currents of Nerve with the Cathode Ray Oscillograph.**

*H. S. Gasser and Joseph Erlanger, Am. J. Physiol., 62:496, Nov. 1, 1922.*

The instruments which have been used heretofore for the observation of nerve action currents have been galvanometers of the moving coil or magnet type, with or without the aid of a rheotome, the capillary electrometer and the string galvanometer. Each of these instruments possesses considerable inertia. The slower galvanometers are unaffected by single action currents and give a sustained deflection when the action currents are monophasic and rapidly repeated. The size of the deflection is the mean value of the individual waves, which in turn depends upon their shape and the rate at which they are repeated. As the former is not known the deflections are mainly of qualitative significance. The string galvanometer record gives the most nearly correct picture of the action current, but no sufficiently accurate means are available for correcting the curve to its true form. While the capillary electrometer shadow is much farther from the true form than the string galvanometer shadow, it can be very much more readily corrected, since, when the electrometer is properly made, the effect of the first or acceleration term becomes negligible and therefore the characteristic is the well-known logarithmic curve without any initial upward concavity in the record produced by a constant current, thus making possible the simple correction as developed by Lippmann, Hermann, Burch, Einthoven and others. The best of the corrected nerve action currents have been made with this instrument.

The low voltage cathode ray oscillograph offers a means by which nerve action currents can be easily and accurately recorded. It consists essentially of a three-stage amplifier, giving a 7000-8000 amplification, working into a Braun tube. The method is possible because nerve action currents can be repeated with great precision 20 times per second, and the record appears as a standing wave on the screen of the tube, where it may be drawn or photographed. There is a special apparatus for synchronizing the nerve potential changes recorded on the ordinate with the movement along the abscissa. The rate of movement along the abscissa is controlled by a condenser and resistance, and can be made very rapid. In the authors' observations the action current was found to have a gradual start, a steep smooth anacrotic limb and a more gradual catacrotic limb, both of which showed a period of great initial acceleration so the crest was situated near the anacrotic side. In frog nerves and some mammalian nerves there were secondary waves on the catacrotic limb.

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**The Chemical Transmissibility of the Effect of Nerve Irritation.**

*R. Brinkman and E. van Dam, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:66, Sept. 27 1922.*

Potassium acts on the heart like vagus irritation. Vagus irritability is increased considerably by small amounts of K ions. It cannot be maintained, however, that liberation of K ions is demonstrated by vagus irritation, nor are the various other views on K ions in the process of nerve irritation as yet sufficiently substantiated. Their action seems to be determined by the reaction:  $K : Ca$  (Loeb). Loewi considers the substances formed in vagus irritation as organic and though cholin itself was excluded, 'cholin-like or muscarin-like substances might be concerned, while substances pharmacologically related to adrenalin might be involved in sympathetic irritation. The 2 factors (the influence of the quotient  $K : Ca$  and of the aforesaid organic substances) mutually influence each other, since it is known that the concentration of K ions and Ca ions is of determinative importance for the action of cholin, adrenalin, etc. It might be assumed that an increase in the quotient  $K' : Ca'$  would be attended by increased parasympathetic, a decrease by increased sympathetic irritability, though no strict proofs of this could be furnished. The latest researches on the pathogenesis of latent and manifest tetany point to a combined irritation by ions and biologic substances (influence of calcium diminution; significance of dimethyl guanidin). An investigation of the possible chemical agents formed as a result of nerve irritation must take into consideration the ionic concentration as well as the production of organic nerve irritants. In order to exclude all hydrodynamic influences from the repetition of O. Loewi's experiments, a decapitated frog's stomach was selected as the reacting organ. The perfusion liquid was introduced into the vena cava of a frog and after its passage through the heart of this animal it was led through a cannula direct into the gastric artery of the experimental animal. The stomach movements were recorded graphically by means of a stomach tube and pneumatic

transmission. The perfusion liquid was a solution with a constant H and Ca content. The KCl varied from 0.005-0.02%. In this manner experimental proof of the existence of a humoral transmission of the nerve action was furnished. Vagosympathetic irritations of the first frog induced typical gastric contractions in the second animal, while irritations with a sympathetic effect on the heart of the first animal resulted in distinct arrest of gastric movements (corresponding to sympathetic irritation) in the second animal.

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**Studies on the Visceral Sensory Nervous System. XIV.  
The Reflex Control of the Cardia and Lower Esophagus in  
Mammals.**

*A. J. Carlson, T. E. Boyd and J. F. Percy, Arch. Int. Med.,  
30: 409, Oct. 15, 1922.*

The literature on the reflex control of the cardia and esophagus is meager in view of the importance of the question in connection with spasms of the cardia and esophagus in man. It has been shown by Carlson and Luckhardt that the cardia and lower end of the esophagus are provided with motor and inhibitory efferents both via the vagi and splanchnic nerves. In the present study the method used with cats and dogs was essentially the same as in the work on the innervation of mammalian cardia. One dog was provided with a permanent gastrotomy and esophageal fistula in the neck, and was used for experiments without anesthesia. All acute experiments were done under light ether anesthesia, or such anesthesia continued with curare, or by decerebration without further anesthesia. Definite reflexes were obtained in all preparations, but light ether anesthesia alone yielded better results.

It was shown that in normal dogs, not under anesthesia, tonus of the cardia may be temporarily inhibited by stimulation of sensory nerves in mouth or pharynx, and by stimulation of nerves in the gastric mucosa, while the tonus of the cardia may be increased by sudden distension of the walls of the stomach, or by the intravenous injection of small quantities of cocaine, and that the tonus is increased during digestion by some factor other than the gastric acidity, and that the tonus runs parallel with the tonus and hunger contractions of the empty stomach.

In animals under light ether anesthesia, ether and curare, or decerebration, it was seen that reflex inhibition or contraction of the cardia and lower esophagus could be initiated by stimulation of any skeletal or visceral sensory nerve; that stimulation of the sensory nerves of mouth, pharynx, esophagus and gastric mucosa in the presence of intact vagi usually induces inhibition of the cardia followed by contraction; that stimulation of the afferents from the abdominal viscera usually causes reflex contraction of the cardia and lower esophagus even after section of both vagi; that, in general, when the tonus of the cardia is feeble, motor reflexes into the cardia prevail, but when the cardia is hypertonic, inhibitory reflexes predominate; and that strong stimulation of abdominal viscera or the central end of the splanchnic nerve may cause strong spasm of the cardia and lower esophagus lasting 10-30 minutes.

The demonstration of motor and inhibitory innervation of the cardia and lower esophagus via the splanchnic nerves and the confirmation and extension of Openchowski's observations on the reflex control of these, should be taken into account in clinical cardiospasm, but there is a long step between these types of spasm in normal animals and cardiospasm in man.

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**The Vegetative Nervous System. III. The Influence of the Vestibular Apparatus on the Vascular System.**

*E. A. Spiegel and Th. D. Demetriades, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196: 185, Oct. 7, 1922.*

Only isolated references exist regarding vegetative reactions due to excitation of the labyrinth. Experiments on the behavior of blood pressure in 55 rabbits showed that excitation of the terminal vestibular apparatus with cold and warm water, as well as galvanic stimulation, caused distinct lowering of blood pressure which may persist up to 50 seconds. Sometimes lowering is followed by a slight rise above the normal level. Lowering of blood pressure sets in a few seconds sooner than nystagmus, the termination of which occurs usually, though not always, before the renewed rise of the pressure curve. That the sensibility of the trigeminus does not participate in this effect was proved by comparisons with the effects of caloric stimulation from the conjunctiva and by inability to influence the reaction by means of intracranial division of the trigeminus. The latter was performed from the membrana atlantoöccipitalis. But a stimulation of the fibers of the tympanic plexus, which course centripetally with the intermedius nerve, might also be concerned. Therefore a stimulus had to be selected which would make it possible to exclude the concomitant excitation of such tracks. For this purpose the experimental animals were fixed to a board which could be rotated about a longitudinal axis, the registration of blood pressure being made possible by means of a tube which turned in a second tube into which it was accurately fitted. These experiments, as well as others performed under methane-ether anesthesia, showed only unequivocal lowering of blood pressure, even in labyrinthine excitation by rotation. Minimal stimuli appear to influence blood pressure, while increased stimulation may diminish this action. The second rise of the blood pressure curve takes place much more slowly than the fall, and not infrequently a higher level than existed before the experiment is attained. This phenomenon is explained as a secondary induction in Sherrington's sense. This depressor reaction does not depend on peripheral effects because it is absent after the centrifugal paths of the vestibular reaction are interrupted. Bilateral exclusion of the labyrinth through injection of cocain causes disappearance or considerable diminution of the blood pressure reaction. On the other hand, the initial rise in pressure, sometimes observable in the normal animal, is preserved. The effect of labyrinthine excitation does not take place through the cardiac nerves, as it is maintained in bilateral vagotomy. Dilatation of the vessels of the head plays only a subordinate part, inasmuch as division of the cervical sympathetic has hardly any influence on the reaction. Obviously the chief factor is a dilatation of the abdominal vessels, because



splanchnicotomy destroys the effect. But, if blood pressure be maintained at the old level after ligation of the aorta and prevention of flow into the splanchnic region, the depressor reaction occurs; therefore other vascular regions must participate in its production.

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**Mesenteric Reflexes on the Heart.**

*W. H. von Wyss and N. Messerli, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:229, Oct. 7, 1922.*

Experiments on the frog have shown that mechanical stimulation of the mesentery occupies an exclusive position as against other possible stimulations inasmuch as cardio-inhibition always takes place without accompanying symptoms on the part of the skeletal musculature such as pain stimuli. There seems to be involved herein a special afferent quality whose physiologic effect should be sought in the region of the abdominal cavity itself, while the effect on the heart can be explained purely by encroachment of the excitation on the cardiac vagal center, as in irradiation. The literature contains a few references to analogous relations in warm-blooded animals which are supplemented by the authors' experiments on decerebrated guinea-pigs (exclusion of pain stimuli). These experiments demonstrated the existence of reflex relations between abdominal viscera and heart in mammals also. The effects on the heart lack legitimacy; this is manifested also by the fact that relaxation of the pulled mesentery may at times produce a cardiac effect that does not apply to the pull itself. Possibly the special experimental conditions may have caused a displacement of irritability in the vagal or accelerator system so that mere application to the conditions in the normal animal is not justified. In no case, however, is it possible for previously nonexistent reflex relations to be produced by these experimental conditions.

Therefore, a fundamental importance for certain cardiac symptoms arising under pathologic conditions in man may be conceded to these experiments, particularly in the case of the sudden cardiac paralysis in abdominal operations, which presents itself as reflective cardio-inhibition. These researches merit the clinician's interest, as bradycardia and tachycardia, as well as induction and abolition or augmentation of heart-block, may be induced from the mesentery by mechanical stimuli. It would be important also to gain a knowledge of the influence of anesthesia, whose deepening might perhaps obviate reflective arrest of the heart's action.

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**Bilateral Vagotomy in Guinea-Pigs.**

*L. Giusti and B. A. Houssay, Rev. Asoc. méd. argentina, Buenos Aires, Biol. Sect., 35:81, May-June, 1922.*

Section of both branches of the vagus in guinea-pigs prevents the arrival, at the bulbus, of the sensory stimuli necessary for regulation of respiration, and produces, successively, bradypnea, convulsive inspirations, long apneic periods, tachycardia, pulmonary congestion, resulting in edema, asphyxia, muscular and nervous exhaustion, and

death. Ozorio de Almeida holds that death is due to irritations produced in the vagus by the cut of the scissors—irritations causing respiratory disturbances. Functional section of the nerves by means of tampons of novocain (1-2%), enveloped in rubber and left permanently, merely caused, in his experiments, diminution of respiratory rhythm, without serious dyspnea. Death did not ensue for 10-12 hours, after resorption of the anesthetic, and was, he thought, due to irritation.

The authors have proved that Almeida's results were due to insufficient anesthesia of the nerve. They have succeeded in causing immediate dyspnea and death by functional sectioning with cold, ether vapor, electrotonus, or novocain anesthesia. With novocain 1% and 2.5%, the deaths were in each series 4 among 7 animals. With novocain 5% and 10% in 2 other series, all the animals died, dyspnea arriving in 1-2 minutes, death ensuing after a period varying from 40 minutes to 3 hours in 12 animals, from 7 to 9 hours in 3 animals. The rubber strips are an absolute necessity for the success of the experiment, to prevent the diffusion of the anesthetic, or its mixing with the blood. Anesthesia of a single vagus branch did not cause death,

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**The Origin of the Electric Change in Muscle.**

*B. A. McSwiney and S. L. Muchlow, J. Physiol., London, 56: 397, Oct. 18, 1922.*

The authors remark that if the electric change in muscle is due to the liberation of lactic acid (as some observers have thought) then the total, measured electric change ought to behave in the same way as the heat production, if the experiments are performed under identical conditions. By employing a sensitive, moving-coil, mirror galvanometer, connected to an injured and an uninjured spot on a muscle suspended isometrically and stimulated through its nerve, it was possible to note the electric effects accompanying a prolonged contraction. The authors studied the relation between the duration of the stimulus and the total electric change, as well as the relation between the frequency of stimulation and the total electric change, recording the results graphically. The curves show (1) that the electric changes which occur in a muscle on contraction do not bear any quantitative relation to the production of lactic acid and (2) within the limits of these experiments, the total electric change in a stimulus of fixed duration is proportional to the frequency of stimulation.

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**The Effect of Splenectomy on Integration of Muscular Movements in the Rat.**

*D. I. Macht and E. M. Finesilver, Am. J. Physiol., 62: 525, Nov. 1, 1922.*

In the authors' experiments rats were trained to walk across a taut rope and their muscular coördination before and after splenectomy was carefully noted. All of the 50 rats included in the study were from 45 to 50 days old at the beginning of the investigation, and it

required on an average 50 days or 50 trials for each animal to master the problem completely and perfectly. When the animals could cross the rope without slipping or swaying, the nature of the muscular integration and the running time across the rope were noted for a period varying from 10 to 20 or more days and the average running time computed. The animals were then operated on (splenectomy) and after recovery were retrained for the rope for a brief period of time and their muscular integration and running time were again noted. Some of the control animals were left intact, while on others was performed a laparotomy with an exploration of the viscera but no splenectomy. The authors' results show that splenectomy improved the muscular integration of the rats and shortened the running time.

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**Weber-Fechner's Law in Human Muscular Work.**

*W. W. Efimoff and A. W. Efimoff, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:243, Oct. 7, 1922.*

Weber-Fechner's law has been subjected to research in 2 directions. One group of investigations seeks to deepen the law, the other to extend its applicability to other vital phenomena. In this sense the authors investigated the greatest possible number of flexions of the lower against the upper arm, under varying load, that was attainable by the experimental individuals. The maximum number of contractions remains fairly constant in one and the same individual and fluctuates within narrow limits from day to day. Eighty-seven individuals were examined. If the weight be designated the "stimulus" and the number of contractions the "excitation," and if the observed results be plotted in accordance with Fechner's fundamental formula:  $A$  (degree of excitation) =  $\log X$  (stimulus) so that the logarithms of the lifted weights are entered on the abscissa and the number of contractions during 5 seconds on the ordinate, an almost rectilinear curve will be obtained. Only the value of the unloaded arm's movement, owing to too small stimulation, causes deviation. No proportionality exists between the number of contractions and the length of the lifting forearm. The amount of work, obtained by multiplying weight by number of contractions per second, yields the work per second, which is likewise dependent on the logarithms of the lifted weights. Deviations were found only in the lifting of small weights by individuals possessing specially powerful musculature.

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**Researches on Muscle Hardness. A Generally Applicable Method of Determining Physiologic Hardness.**

*Ernst Mangold, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:200, 215; Oct. 7, 1922.*

The new sclerometric method consists essentially in measuring by means of a lever the compressibility of the isolated muscle as well as of that in situ. In order to obviate the use of absolute values the percentage alteration of compressibility is calculated and recorded by

curves. As the percentage decrease of compressibility diminishes under the influence of increased lever load the values for different muscles are comparable only when obtained with the same load. The isolated muscle's lever load and tension most suitable for measurement must be determined (10-20 gm. load; the results are the same with tensions of 50, 500 and 1000 gm.). The secondary elastic effect also plays a certain rôle, both in the depression of the pressure pad on the muscle's surface and in the abolition of the deformation, though this factor is of little importance with high muscular tension. Repeated measurements on one and the same muscle and on 2 symmetric muscles of the same animal serve to determine the degree of accuracy of the method. The method itself has no material influence on the hardness of the muscle.

The sclerometer was adjusted by means of a glass tube, which the pressure pad fitted accurately, and which was continuous with a mercury manometer, thus permitting the lever load to be calculated as pressure values. Gelatin cylinders are also suitable test objects. Further investigations embraced the influence of the support and of the object's thickness. The latter, at least in objects of the dimensions of a rabbit's triceps muscle, are of no significance. The method is applicable also to other organs besides muscles.

The new sclerometric method permits the hardness arising in conditions of rigor and the time of its production to be followed metrically. The experiments were performed on rabbits' muscles and also partly on those of cats and guinea-pigs, namely on the musculus triceps surae, which is specially suited to this purpose. In rigor mortis hardness begins to increase only 3 hours after death and attains its maximum after 24 hours. Contrary to shortening of the rigor mortis muscle, which is absent at times, postmortal hardening appears to take place regularly. Similarly, in heat rigor, shortening and hardening are widely independent of each other. In the rabbit's musculus triceps surae a shortening stage is found in the course of heat rigor at 52-58° C. and a second one commencing at 62° and ending at 68°. These stages are designated primary and secondary heat rigor. In the first, shortening amounts to 13-20%, in the latter to 42% of the initial length. In the first heat rigor the muscle is as yet barely clouded, in the second it assumes a whitish turbid appearance as if it had been boiled. On the other hand, the hardening attained in primary heat rigor is not altered by the secondary stage. Hence, a difference in the muscle's internal changes that condition primary and secondary heat rigor probably exists or participation of different tissue elements is involved.

The time that has elapsed since death is of no consequence when comparing the degree of increase in hardness induced by heat rigor to the initial values in the fresh muscle but that does not apply to the state of hardness conditioned possibly by already preëxistent rigor mortis. This may remain the same on heating or may be diminished thereby. A heat rigor muscle does not alter its degree of hardness even when observed for some days, that is, when once rendered rigid by heat it cannot then assume cadaveric rigidity. And a rigor mortis muscle is unable to assume heat rigidity, owing to increased hardness but not owing to shortening. Heat rigor exercises an influence only during the uncompleted increase of rigor mortis.

## URINARY SYSTEM

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### **Partial Activity of the Kidney and the "All or Nothing" Principle.**

*V. R. Khanolkar, J. Path. & Bacteriol., Edinburgh, 25:414, Oct., 1922.*

The author reviews the history of the "all or nothing" principle which physiologists now claim is applicable to all excitable tissues. He considers the various organs of the body as composed of units, the units of the particular organ responding to stimulation by rotation, so to speak, some active, some completely refractory and others relatively inexcitable. With increasing strengths of stimulation successive groups are brought into action, first those whose active spell is most remote and finally those in which it is most recent. By this means a larger number of units than is usually necessary is kept in efficient working order. In the present work the author sought to obtain anatomic evidence of activity of some units during moderate activity and of all units during extreme action of the organ (kidney). The method employed to obtain evidence of the focal secretory activity of the kidney consisted in observing the distribution of easily recognizable substances (iron salts, carmin, hemoglobin) eliminated by the healthy kidney, after their introduction in the blood stream. Using a solution of iron-ammonium citrate in doses of about 0.4 gm. per kilo body weight and killing the animals after 3-5 minutes, the presence of iron-containing particles in the cells of the convoluted tubules was demonstrated.

In specimens that were fixed in alcohol presence of iron histologically in the capsules of the corresponding glomeruli could not be demonstrated. The uneven distribution of iron may indicate the selective action of certain tubules in the secretion of iron, or may indicate the substance was present in the units of the kidney which were functionally active at the particular moment when the animal was killed. For the experiments with carmin this dye was dissolved in lithium carbonate solution and then introduced into the blood stream. Subsequent examination of the animal's kidneys showed a faint pink stain of all the glomerular capsules. Some glomeruli showed "worm-cast" deposits of stain in their capillaries. These experiments indicate that at any one particular moment all the glomeruli are not alike, at least so far as their circulation is concerned, as some of them contained the "worm-cast" deposits of stain and others did not. Following injection of solutions of hemoglobin, if the kidneys are fixed in boiling water, the hemoglobin in fresh, unstained thick sections is found coagulated into a yellowish reticular crescent, distending the space round the glomerular tuft. Sections stained with eosin and counterstained with methyl-green showed these masses of hemoglobin clearly.

The author concludes that the various units of which the kidney is composed are not all active during moderate activity of the organ. Active units are active to their utmost capacity. Increased demand is met by an increased number of units being thrown into activity, not by increased activity of the active units.



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**The Renal Function as Judged by the Excretion of Vital Dye-Stuffs.**

*J. de Haan, J. Physiol., London, 56:444, Oct. 18, 1922.*

In the author's experiments previously catheterized male rabbits were given intraperitoneal injections of one of the dyes to be studied (fluorescein-potassium, phenol red, indigocarmin, lithium-carmin, trypan-blue and trypan-red). At different moments after injection 1 c.c. of blood was collected in a graduated centrifugal tube, containing 3 c.c. 0.7% NaCl solution and 1.1% sodium citrate. After centrifugalization the dye concentration was determined, taking into account the dilution by the citrate and the volume of the blood-corpuscles. Immediately before the injection of the dye, and at the end of the experiment, 4.5 c.c. blood were collected in about 0.5 c.c. 10% sodium citrate solution and centrifugalized. The plasma thus obtained was filtered in a micro-ultrafilter of de Ward, the urea in the ultrafiltrate was determined in both portions, and in the latter the percentage of dye was also estimated. At various intervals after the injection of the dye, catheter-collected urine was examined for dye and urea. By the above procedure it is possible to estimate (1) the concentration of the dye present in the blood-plasma during a certain period; (2) the concentration at which such a dye concentration could pass from the blood-plasma into a glomerulus filtrate, free from colloids; (3) the minimal inspissation of the glomerulus filtrate in the tubules, based on the concentration of dye in the urine. The author's results show that by far the greater part of acid vital dyestuffs is adsorbed to the colloids of the blood-plasma. On the ground of this adsorption union with colloids, the primary glomerular filtrate cannot be free from protein; but must contain the plasma colloids, though perhaps in lower concentration. Urea and other substances must, judged by the course of dye secretion, be reabsorbed in a rather great degree by the cells of the convoluted tubules. Thus excretion of all substances normally not present in the blood is accounted for, the tubular cells having no affinity for substances with which they have never been in contact.

**ENDOCRINE GLANDS**

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**The Biologic Significance of Endocrine Organs.**

*C. Hart, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:127, Oct. 7, 1922.*

Gudernatsch found that thymus feeding stimulates powerfully the growth of tadpoles, but retards or arrests metamorphosis, while, conversely, thyroid feeding accelerates metamorphosis but arrests growth almost entirely. These experiments give rise to a series of hitherto unheeded questions: (1) the nature of the active substances, which problem has been studied by Abderhalden; and (2) the question of the attacking point of the active substances. They may act directly or by intermediation of endocrine organs. The author was able to confirm Gudernatsch's results by effecting arrest of growth in young axolotl by cauterizing the thymus. But in thymus-fed tadpoles further

phenomena manifest themselves which point to complicated effects, namely, swelling of the animals owing to increased water content, so that they at times assume a spherical shape. This swelling, similarly to that in myxedema in man, is to be referred to hypofunction of the thyroid gland. The arrest of metamorphosis is obviously not merely an effect of thymus feeding but also of diminished thyroid function. In view, however, of the manifold reciprocal effects of the endocrine organs, all these must be investigated.

The influence of the endocrine system is obviously related also to the conversion of the neotenic adolescent form into the salamander form, because in axolotl, as in tadpoles, metamorphosis can be effected by means of thyroid substances, very small quantities sufficing for that purpose. In these animals apparently a hereditarily fixed pluriglandular formula obtains which arrests the metamorphic thyroid function. In the metamorphosis brought about by thyroid feeding the branchial ridges disappear; the large paddle-tail or the long dorsal crest becomes involuted; and the head and trunk undergo transformation. Further, all metamorphosed axolotl show exophthalmos and prognathism, the former depending probably on thyroid feeding, the latter on metamorphosis of the head. Finally, noteworthy displacement of pigment takes place under repeated desquamation, and by means of repeated thyroid administration the shedding can be produced again and again. The metamorphosed axolotl are smaller and lighter than the larval form chiefly owing to deficient nutrition. The course of metamorphosis is ontogenetic and phylogenetic under the dominating influence of thyroid function, on which the external factors influencing metamorphosis (for instance temperature) act. Thereby a connecting link is obtained between the theory of environmental influence and that of the significance of endogenous factors in metamorphosis. A conversion of the external into internal forces, attended by refinement and specialization, takes place. Thereby the organism is enabled to adapt itself to the vital conditions of the surrounding world. The vital and developmental capacity of the animals here considered is founded chiefly on this law of the conversion of external into internal forces by endocrine organs.

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**The Biologic Significance of the Endocrine Organs. II. The Influence of Abnormal External Temperatures on the Thyroid Gland and Testicles.**

*C. Hart, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196: 151, Oct. 7, 1922.*

Ontogenesis and phylogenesis are subject to the influence of external vital conditions, whose action is unfolded by the conversion of external into internal forces induced by the instrumentality of the endocrine organs. This influence of the endocrine apparatus and its action of inducing manifold morphologic and functional disturbances is recognizable in man. The influence of climate and season is manifested first in the region of the endocrine organs. Experimental analysis must separate the individual active factors from the complex climatic factor. Unquestionably temperature plays a prominent rôle herein. Gray

house mice, kept at room temperature to commence with, were subjected to high temperatures of 32-40° C., or low ones of 4-7°. With high temperatures the size of the thyroid was greatly reduced, the follicles were extremely poor in colloid, collapsed, or provided merely with a narrow, cleft-shaped lumen; the protoplasm was homogeneous. Mice kept at abnormally low temperatures possess well-rounded follicles filled with colloid which stain darker than the normal and appear denser, and cubical epithelium with numerous secretion vacuoles. These changes are balanceable and reversible. Thus, under the influence of temperature, considerable fluctuations of thyroid function take place, attended by far-reaching modifications of total metabolism and heat regulation. Adler's researches have also demonstrated the existence of a relationship between thyroid function and hibernation. Other factors besides temperature influence the thyroid glands (one-sided nutrition).

Temperature variations cause remarkable changes in the male genital glands. Considerable temperatures produce severe degenerations of the seminiferous cells, the injury progressing from the internal, more matured layers toward the outer ones. Finally, the specific parenchyma undergoes almost complete destruction. This injury also is balanceable. These changes are the expression of a requirement that plays a rôle under physiologic conditions and which is regarded as a part-phenomenon of the prevailing adjustment of the endocrine system. The change probably originates through the direct action of heat on the genital gland's tissue. In connection with this parallel thyroid and testicular injury, it is worthy of mention that among poisons injurious to the testicle, iodine plays an important part. The correlation between the thyroid gland and the testicles is, therefore, regarded as a purely chemical one. It is conceivable that non-radical changes might give rise to an altered sexual product as well as to changes in the characters of the progeny. The germ-cells are undoubtedly subject to the influence of internal secretions, which renders intelligible the influence of external vital conditions on the hereditary substance in the sense of an alteration and opens an avenue of approach to the explanation of the transmission of acquired characters.

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### **The Physiology of the Pineal Gland.**

*W. Kolmer and R. Löwy, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196: 1, Sept. 27, 1922.*

In young rats, the pineal gland was destroyed through the cranial vault with a small thermocautery. In very young animals, the gland may be removed without injury of any kind. In the rat the loss of the pineal gland causes no detectable changes in fat production or sexual precocity, so far as this is determinable. Following castration neither macroscopic nor microscopic examination disclosed any signs of pineal injury that might be referred to loss of the gonad hormones. Although experiments cannot yield indications of the organ's functional significance, a conclusion can possibly be drawn from anatomic studies. From the habenal and posterior commissures, fibers pass into the anterior portion of the gland and enter into relation with the pineal

cells and marginal plexuses. The course of these fibers is described exactly with the aid of a sagittal series in a 3 months old male goat. In the dog, the monkey and in man medullated fibers are also detectable below the connective tissue enveloping the pineal gland, which differ from Marburg's nervi parietales arising in the habenal commissure and are designated as nervi conarii by the authors. In the adult animal these nerve trunks possess medullated fibers with Schwann's sheaths. They are connected with the venous system into which the veins of the choroid plexus enter. Thus, the pineal gland and the aforesaid nerve may form a system which would be capable of influencing the circulatory conditions in the plexus and thereby the secretion of cerebrospinal fluid. The correlation between development of the pineal gland, plexus and ventricle in the animal order also suggests that the cerebrospinal secretions are regulated by the pineal gland, which regulation would take place, at least in some mammals, by means of the described nervi conarii.

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**Suprarenal Studies.**

*Hans Kutschera-Eichbergen, Frankfurt. Ztschr. f. Path., Munich, 28: 262, Nos. 1-2, 1922.*

Adrenalin reduces ammoniacal silver solutions in the tissues as it does in vitro. This reaction forms the basis of the histologic demonstration of adrenalin. Adrenalin is secreted as a fluid from the medullary cells of the suprarenals. It can also be demonstrated histochemically in many cases in the cortical capillaries of the suprarenals. The suprarenal of mammals, like that of birds and reptiles, has a double venous supply. The distribution of blood and adrenalin in these 2 venous systems is regulated in man and in other mammals by the muscular contracting system of the medullary veins. In mammals the same intimate relation between the medullary and cortical tissue is brought about by the circulatory conditions as is accomplished in the lower vertebrates by the interlacing of the 2 kinds of tissue. The capsular veins of the left suprarenal communicate with the veins of the pancreas and also with the portal vein. The histochemical and anatomic findings and the pathologico-anatomic pictures in the suprarenal in connection with known experimental and clinical observations make it probable that the forcing of adrenalin into the suprarenal cortex and the capsular veins by the action of the muscular constrictors of the medullary veins has a functional importance, especially in sugar metabolism. The chromaffin substance is characterized by its physical and chemical properties as an emulsion colloid; it may represent the cell ferment that is theoretically necessary for the formation of optically active adrenalin, but which has not heretofore been demonstrated.

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**The Organic Functions of Dogs Deprived of the Medullary Portion of the Suprarenals.**

*B. A. Houssay and I. T. Lewis, Rev. Asoc. méd. argentina, Buenos Aires, Biol. Sect., 35: 55, May-June, 1922.*

Houssay and Lewis have proved in previous reports that dogs will survive after the removal, in 2 sessions, of the medullary substance

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of the left suprarenal and of the whole right gland, provided enough of the cortical substance from the left suprarenal remains. After a new series of experiments on dogs, giving similar results, the writers conclude that dogs deprived of the suprarenals but maintaining the cortical substance on one side, live on in excellent health; but they will die, showing the usual symptoms and at the usual time, after the removal of the remaining cortical substance. In the former case the temperature is kept normal or slightly increased; the arterial blood pressure and the blood composition are also normal; there is no asthenia, pigmentation nor hyperexcitability; the vascular reaction to adrenalin and pituitary extracts is normal as well as the pupillary reactions to cocain, atropin and adrenalin.

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**Studies in Fatigue. XII. The Effect of Adrenal Secretion on Nonfatigued and Fatigued Skeletal Muscle.**

*Charles M. Gruber, Am. J. Physiol., 62:438, Nov. 1, 1922.*

The author has shown that adrenalin, when injected intravenously, has the same effect upon nonfatigued muscle as it has upon fatigued skeletal muscle. This present work was undertaken to see if secreted adrenalin, evoked by splanchnic stimulation, had the same action as the intravenous injection of moderate or massive doses of adrenalin. Cats under ether anesthesia were used. The general experimental procedure was the same as that employed by the author in the previous work. The time interval in all cases was 30 seconds. The rate of stimulation was 35 stimuli per minute for the fatigued muscle and 3 stimuli separated by periods of 10 seconds followed by a rest of 1 minute for the nonfatigued muscle. Both muscles were after-loaded by 50 gm. The resulting myograms show that adrenal secretion evoked by splanchnic stimulation increases the height of muscular contraction of both the nonfatigued and fatigued skeletal muscle. The quantity of adrenalin secreted must be fairly large, judging from the height of betterment and the duration of improvement when compared with the results from injections of adrenalin intravenously. As adrenalin secreted by splanchnic stimulation affects nonfatigued and fatigued skeletal muscles alike, it cannot be regarded as a specific antagonist to the so-called fatigue substances. By an unknown mode of action it increases the height of contraction and irritability of both muscles.

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**The Action of Adrenalin on Striated Muscle.**

*J. Guglielmetti, Rev. Asoc. méd. argentina, Buenos Aires (Biol. Sect.), 35:126, July-August, 1922.*

It is an undisputed fact that adrenalin improves the contraction of a fatigued muscle. This is easily demonstrated in frogs. The height of the recuperation is, in general, less than that of the original curve, but under appropriate dosage and weight with which the muscle is charged it is possible that it may be greater. With the current technic, no double recuperations have been found in frogs. The curve of recuperation is modified by (1) amount of adrenalin, (2) frequency of



stimuli, (3) weight raised by the muscle, (4) promptness with which the product acts when fatigue is visible. The form in which the stimulus is applied (direct or indirect) does not affect the phenomena. To test the action upon muscle not fatigued, care was taken to excite the muscle with a current of low intensity, obtaining a contraction of medium height. Adrenalin was seen to improve the height constantly. To test the effect upon muscle from which the nerve had been excised, 1 cm. of the gastrocnemius in frogs and of the tibialis anticus in dogs was removed. The effect in both animals was similar. Adrenalin injected in the abdominal vein of the frog not only produced no increase of the curve, but even diminished it. In the dog, the adrenalin is injected into the artery, to avoid hypertension, which, it is known, increases the curve. If the animals are curarized, adrenalin exercises no effect at all upon the muscle, fatigued or otherwise. In the light of these experiments, it seems that adrenalin acts upon the intermediary substance, and that, according to Langley and Lewis, it should be met with at the point of union of muscle and nerve.

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**The Rôle of Adrenalin in the Effects Produced by Excitation of the Splanchnic Nerve or by Bulbar Puncture.**

*B. A. Houssay, Rev. Asoc. méd. argentina, Buenos Aires, 35: 131, Biol. Sect., July-Aug., 1922.*

In 1919 the author demonstrated that hypertension produced by excitation of the splanchnic nerve is due to 2 factors: direct vasoconstriction and the action of the segregated adrenalin. His experiments were made on 52 dogs, under chloral anesthesia (neither ether nor curare will answer). The technic was that of V. Anrep. Approaching the left suprarenal by the posterior retroperitoneal route, the author dissected away the lumbocapsular vein before and behind the gland, which permitted the clamping and unclamping of the vessel at will. The left splanchnic nerve was cut where it left the diaphragm, and was stimulated electrically. Then the carotid pressure was inscribed, and the plethysmogram recorded of a posterior flap denervated by section of the sciatic and crural nerves. A portion of the plethysmogram is reproduced. In 95% of cases a greater elevation of pressure was produced when the veins were free than when they were clamped. Strong excitation of the nerve, with the vein clamped, made the pressure become unstable, and upon removal of the clamp the pressure was seen to rise and reach the same level as in the excitation with veins free. In the denervated flap, when the veins were free, an initial passive dilatation was observed, followed by a marked contraction, due to adrenalin; when they were clamped, the dilatation alone was seen; upon removal of the clamp, there was dilatation followed by contraction. The effect was seen best when an excitation of medium intensity was used.

In similar experiments, the author showed that bulbar puncture in dogs well prepared (removal several days before of the right suprarenal, the medulla cut at the twelfth dorsal vertebra, the denervated flap well exposed, artificial respiration and bilateral vagotomy) produces strong hypertension. The same phenomena are observed relative to use of clamps. In more recent experiments he has shown that dogs live

despite the removal of the medullary substance of the left suprarenal and, afterward, of the whole right suprarenal. The latter experiments show that the adrenalin of the medullary substance is not necessary for conservation of the vascular tone. Notwithstanding this, the experiments here described show that under special conditions (excitation of the splanchnic nerve or bulbar puncture) there is produced a discharge of adrenalin that has real effects. It is probable that under physiologic conditions it is also produced, at least under conditions of emergency, and plays a coadjuvant part.

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**The Influence of Adrenalin on Metabolism in Various Excised Tissues.**

*E. G. Martin and R. B. Armitstead, Am. J. Physiol., 62:488, Nov. 1, 1922.*

In previous experiments the authors demonstrated that the production of carbon dioxide in excised skeletal muscles of the frog is markedly augmented by the addition of adrenalin to the solutions in which the muscles are immersed. The interpretation of those findings was that adrenalin exerts a thermogenic influence upon living tissue. They now record the extension of their previous experimental procedure to brain tissue, mesonephric tissue, and liver, stomach and intestinal tissues of the frog. As it was not necessary, in this study, to insure absence of contraction of these tissues, they were simply lowered into tubes containing the solution and indicator, and stoppered tightly with paraffined corks.

The authors expressed their results in terms of acid production per gram of tissue per hour, the computations being made according to the following formula:  $A_c = 60 C_H \div w t$ ,

in which  $A_c$  is the calculated acid production,  $w$  the weight in grams,  $t$  the time in minutes, and  $C_H$  the difference between the final and initial pH of the solution. For converting pH values into  $C_H$  the authors used a table adapted from McClendon's chart. They found that frogs' brains, excised from the body and immersed in Ringer's fluid, showed an acid production averaging, per gram per hour,  $95.5 \times 10^{-8}$ , expressed as  $C_H$  at  $20^\circ \text{C}$ . The addition of adrenalin in concentration of 1:200,000 resulted in an average 2.6-fold augmentation. Frogs' mesonephric tissue, under similar circumstances, gave an average acid production of  $17 \times 10^{-8}$ ; adding adrenalin in concentration of 1:100,000 or 1:200,000 resulted in an average 3-fold augmentation. Frogs' liver tissue, also under similar circumstances, gave an average acid production of  $6.5 \times 10^{-8}$ . The addition of adrenalin in concentration of 1:200,000 resulted in an average 2.5-fold augmentation. Frogs' stomach tissue, including both muscular and mucous coats, gave an average acid production of  $141 \times 10^{-8}$ ; adding adrenalin in concentration of 1:200,000 resulted in an average 1.6 fold augmentation. Frog's intestinal tissue, also including both muscular and mucous coats gave an average acid production of  $78.5 \times 10^{-8}$ ; adding adrenalin in concentration of 1:200,000 produced a 1.33-fold augmentation. The authors' interpretation of these experiments is that the thermogenic influence of

adrenalin is not specific for any one kind of tissue but extends to most, if not to all, varieties.

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**The So-Called Compensatory Hypertrophy of the Testicle after Unilateral Castration.**

*Alexander Lipschütz, J. Physiol., London, 56:451, Oct. 18, 1922.*

Compensatory hypertrophy of the testicle after unilateral castration has been reported by several observers. The author has shown that on removal of the greater part of both testicles, the small fragments which remain, even when they are less than 1% of the testicle, do not hypertrophy, and are sufficient for the full development of those sexual characters which depend upon the internal testicular secretion. It follows, then, that the hypertrophy which occurs after unilateral castration cannot be due to an increased demand for internal secretion. The author believes this hypertrophy is only an apparent one, due to the development being quicker than normal, since the final weight does not exceed the final weight of the normal testicle.

This opinion is substantiated by experiments on rabbits, 3-8 weeks old, which were subjected to semicastration. This procedure was also performed on adult animals. It was found that the difference in weight between the remaining testicle after semicastration performed at an early age, and that of a normal rabbit, is less the older the animal and the nearer full testicular maturation. In only 1 of 4 unilaterally castrated animals, observed by the author for more than a year, was the weight of the remaining testicle greater than that of any normal testicles observed. When semicastration was performed on adult animals no hypertrophy occurred nor were signs of deficiency of sexual hormones present. These facts clearly demonstrate not only that there is no compensatory hypertrophy of endocrine nature of the remaining testicle, but that there is no hypertrophy at all.

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**Testicular Atrophy Following Extirpation of the Abdominal Sympathetic.**

*N. Takahasi, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:237, Oct. 7, 1922.*

Apropos of the experiments heretofore made on sympathetic innervation of the guinea-pig's skeletal muscles, which showed wholly negative results, other organs besides muscles were subjected to microscopic control to determine the influence on the same of extirpation of the abdominal sympathetic (in the region of the internal 3 lumbar and the upper 2 sacral vertebrae). The experimental organs were kidney, suprarenal gland, ovaries, testicles, skeletal parts of the posterior extremity and arteries. Here, too, with the sole exception of the testicle, all results were negative. This organ gave a significant result as weighing and measurement showed testicular atrophy on the operated side. Secondary injuries, possibly of the spermatic artery, could not be detected. The histologic examination also showed distinct atrophy of the testicle on the operated side whereas with bilateral extirpation of

the sympathetic, either bilateral atrophy or bilateral normal conditions existed. The atrophy is characterized by a diminution of the germinative epithelium without concurrent increase of connective tissue and interstitial cells. The canals may not be collapsed. The wall-covering of the tubules consists of Sertoli's cells which dominate the picture although isolated spermatogoniums and degenerating spermatocytes are found. It is remarkable that animals whose left-sided abdominal sympathetic had been extirpated showed bilateral atrophy so that possibly concomitant injuries to the right sympathetic were concerned.

No definite explanation is possible at present, nor are facts available for explaining the origin of the testicular atrophy. A primary disturbance of vasomotorial innervation might be conceived which is, however, rendered little probable in view of the vasodilator action of sympathetic exclusion. Possibly the phenomena could be explained by the assumption of trophic nerves which, as is well known, meets with great difficulties. Or a disturbance of centripetal conducting fibers could be involved, in accordance with the conceptions of the regulation of tissue nutrition by a specific sensibility penetrating all tissues, as developed by R. W. Hess. In the present case the paths of this chemical tissue sensibility would run in the sympathetic fibers.

## 1b. BIOLOGIC AND ORGANIC CHEMISTRY

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### Ferment Action with Nonferments.

*W. Biedermann, Münch. med. Wchnschr.*, 69: 1402, Sept. 29, 1922.

Starch hydrolysis may under certain conditions be brought about by nonferments. Natural ferments, as a rule, are based on specific organic substances or mixtures of substances, which are not effective in and of themselves but become so in connection with other substances, partly organic, partly inorganic. The chief task of the ferment chemist is to isolate such specific organic fundamental substances in individual cases. The parotid saliva is an excellent material for such studies. It contains a specific protein, the aqueous solution of which has an extraordinarily strong diastatic action. It is possible that this protein is not the basic organic substance of the ferment but only the carrier of an unknown substance to which the enzymatic action is to be attributed. The author succeeded in excluding this theory by showing that artificially prepared albumoses and even amino-acids have a diastatic action under certain conditions. By treating albuminous substances with superheated steam Neumeister some years ago described albumose-like cleavage products as "atmidalbumid" and "atmidalbumose," the characteristic reaction of which showed a marked identity with that of saliva albumose. This led the author to test solutions of atmidalbumose for diastatic action, and he found that there was a particularly strong one. The fact that in a given case the fermentative action is not at all dependent on the integrity of the organic carrier, but is to a certain extent divisible, as it inheres also in cleavage products, seems to the author to be of particular and essential importance. It seems to justify the hope that traces of diastatic action may be found in simpler cleavage products, among them polypeptids and amino-acids.

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**The Demonstration of a Fermentative Solution of Coagulated Proteins by Means of the Immersion Refractometer.**

*Ernst Kupelwieser, Biochem. Ztschr., Berlin, 131:413, Sept. 16, 1922.*

To demonstrate and follow up the processes included under the conception of fermentative catabolism of albumin 3 methods are used. The first works with a solid substrate and a ferment solution (Mett's method). The second subjects the substrate to the action of the ferment in a colloidal solution. The indication here is the loss of some characteristic property of unsplit albumin, such as heat coagulability or precipitability by certain reagents in certain concentrations. Pregl and De Grinis have developed a third method of demonstrating specific serum ferments, the so-called immune or protective ferments in very small amounts of serum, in which a reaction system developing from the solid substrate and from the fluid to be examined for its fermentative characteristics is utilized. The change in the refractive index of the fluid part of the system is observed by means of Pulfrich's immersion refractometer and is taken as a sign that a fermentative action has taken place. This micromethod was also used for the study of other proteolytic ferments and an attempt made to solve these questions: How accurately can the effect observed be defined? Is the change in the refractive index only a function of the amount that goes into solution, or is it also dependent on further catabolism of the already dissolved substrate? What sort of a function of the dissolved substrate does the increase in the refractive index represent? Finally, what conclusions can be drawn as to the concentration of the ferment?

The sources of error were studied and the method worked out quantitatively. The method is carried out briefly as follows: The dry protein used as a substrate is tested for its spontaneous solubility by the refractometric examination of the water in which it is boiled, as well as by a test in the system fluid minus ferment, under the same conditions as those used in the ferment experiment, and is held to be suitable when 0.01 gm. substrate in 0.5 c.c. fluid brings about an  $n_D$  increase of at most 0.00005. For the experiment 0.01 gm. substrate is air-dried and weighed accurately, washed in a test-tube with boiling physiologic salt solution, the tube filled and closed with a glass stopper, placed on a water bath for half an hour and let stand at room temperature. The further procedures take place after a certain interval of time. The salt solution is drawn off and to the substrate is added 0.55 c.c. ferment solution. After being well mixed and after a suitable interval of time part of it is taken for the first  $n_D$  determination. Under the given experimental conditions increases of refractive index beginning with 0.0001 may be assumed to be signs of fermentative action, and the variations in the method that were worked out for quantitative purposes agree under like conditions within a range of error of  $\pm 0.00005$ . It was found that the method with variations up to 0.00150 included only the fermentative dissolving of the substrate, while the catabolism itself was not observed, and that the  $n_D$  increases observed were proportional to the amount of substrate dissolved. It therefore gives a measure of the dissolving of the substrate, which would seem to make the method



adapted for the quantitative study of the fermentative dissolution of coagulated proteins. Finally it is demonstrated how far the method reveals the concentration of the ferment, and to what extent it shows itself sensitive.

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**Peptone Fermentation.**

*Emil Baur and Eugen Herzfeld, Biochem. Ztschr., Berlin, 131: 382, Sept. 16, 1922.*

From the experiments just reported by Schlatter the authors draw the conclusion that the organic fluid does not consist of a fermentative principle which can be withdrawn from the fluid like the fragrance from the rose, and of a dead ballast which can be rejected as an impurity, but that the fluid in toto is the ferment. Nothing can be removed from it, especially not its turbidity. This is the reason why the glycolytic ferment seems to be closely combined with the protoplasm. He agrees with Fodor that the endoferments are not foreign to the ferment, not secondary constituents embedded in the protoplasm, but the protoplasmatic substance itself, but that they keep their activity only so long as they preserve their natural condition. Liebig is therefore right, when he says that the ferment is fundamentally disintegrated, at least it changes its colloidal condition; and Pasteur is right when he says that fermentation is a vital process. The object of vitality is the restoration of the used up ferment.

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**The Tryptophane Content of Some Proteins.**

*Clarence E. May and Embree R. Rose, J. Biol. Chem., 54: 213, Oct., 1922.*

The authors' method depends on the fact that when tryptophan is liberated by heating the protein with hydrochloric acid in the presence of Ehrlich's reagent (p-dimethylaminobenzaldehyd), a reaction takes place resulting in the production of an intense blue color. The tryptophan content of casein was taken as the standard of comparison, an intense blue color suitable for colorimetric comparisons being produced by the amount of tryptophan present in 0.1 gm. casein hydrolyzed and diluted to a volume of 100 c.c. Ehrlich's reagent was found to produce more color when added to the digestion mixture of protein before hydrolysis had taken place. The best conditions for hydrolysis of the protein were obtained when 50 c.c. concentrated c.p. HCl, 50 c.c. water, and 1.0 c.c. reagent were mixed. To this mixture, weighed portions of the protein (0.05-0.1 gm.) were added and the whole incubated at 35° C. for 24 hours and then allowed to stand 24 hours or longer at room temperature. This procedure gave blue solutions, varying only in intensity of color, when tryptophan-containing proteins were hydrolyzed. The authors calculated the tryptophan content of 13 different proteins on the basis that 1.5 gm. tryptophan were yielded by the hydrolysis of 100 grams of casein. The tabulated results compare favorably with results obtained by other workers employing different methods.

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**Nucleic Acid-Albumin Compounds.**

*H. Steudel and E. Peiser, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 298, Oct. 6, 1922.*

By quantitative estimation of thymonucleic acid in nucleoprotamins and in nucleohiston, the remaining albumin component can be determined exactly. By bringing together the calculated amount of sodium thymonucleinate and clupein sulphate, clupein thymonucleinate may be obtained, which is certainly a salt. By comparison with the natural product obtained from the heads of herring spermatazoa no analytic difference is found in the 2 substances, so that the nuclein in fish spermatazoa is actually a salt of thymonucleic acid with basic clupein. As the nucleins from nucleoproteins are said to be formed by cleavage of loosely combined albumin while fish spermatazoa nucleins, which should hold the albumin more firmly, are undoubtedly salts, the view that the nucleoproteins are also salts of nucleic acids with basic albuminous substances is supported. In the case of nucleohiston only a part of the albumin is easily extractable with hydrochloric acid. The composition of nucleohiston is inconstant and depends on the method of preparation. Along with nucleohiston, nucleic acid precipitates a varying mixture of basic albuminous substances and this precipitate also contains histon thymonucleinate. Other salts of nucleic acids with albuminous substances were prepared with the aid of guanylic acid and yeast-nucleic acid and finally with pigments (eosin-clupein).

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**The Asymmetric Action of Emulsion in Benzoöxynitril Synthesis.**

*E. Nordefeldt, Biochem. Ztschr., Berlin, 131: 390, Sept. 16, 1922.*

The cause of the symmetric and synthetic action of emulsin in benzoöxynitril synthesis is not necessarily an enzyme, as Rosenthaler assumes, but may be regarded as a simple acidity action. The specific action of emulsin on a mixture of benzaldehyd and hydrocyanic acid is the production of asymmetry in the oxynitril that develops. Some characteristics of emulsin were studied as well as the optimum conditions for the formation of active d-oxynitril. The development of optical activity was studied by polarimetric examination after shaking with chloroform, and also by direct polarimetric examination of the homogeneous substrate solution. The total amount of oxynitril remains constant, but the optical activity decreases rapidly with time, also with increasing temperature and increasing neutrality. The emulsin used was not prepared by the method of Willstaedter and Csanyi but by Herissey's method, but acetone was used in place of alcohol as a precipitating agent. If benzaldehyd and hydrocyanic acid were mixed in solution in equimolecular amounts, they combined to form benzoxynitril, and the rapidity of this reaction was a function of the hydrogen-ion concentration. This oxynitril is optically inactive. If emulsin is present in this reaction the synthesis is asymmetrical and d-oxynitril is formed. The globulin contained in the emulsin is precipitated in insoluble form and is catalytically inactive. If the globulin takes up benzoic acid from the

substrate this precipitation is prevented, while emulsin is removed by dialysis of the salt content or the reaction mixture is made weakly alkaline. In this way an optically inactive oxynitril is produced, whose amount is dependent on the quantity of emulsin present. With small amounts of emulsin the rotation of the amount of emulsin is proportional to the amount of emulsin preparation, while with large ones it increases more slowly.

The d-oxynitril obtained is labile and the rotation of the solution decreases of itself, without the coöperation of an enzyme or any other catalyzer. The rapidity with which the rotation decreases increases with a temperature coefficient of  $k_{s+10} : k_s =$  about 3.2, decreases with increasing acidity within the field  $\text{pH} = 3-6.5$  and reaches the height of the total rapidity of synthesis only at the neutral point, where both are very great and where the optical rapidity disappears as rapidly as it develops. Rosenthaler's observation that the strongest rotation takes place when an excess of benzaldehyd is dropped slowly into a mixture of emulsin and hydrocyanic acid, is explained by the fact that the acid formed by the oxidation of the aldehyd increases the acidity of the mixture, which in time brings about strong optical activity, because then the rapidity of inactivation is decreased. The same author's finding that emulsin once used no longer causes optical activity in a new substrate, which was regarded by him as injury of the emulsin by the oxynitril, is to be attributed to the fact that the oxynitril has taken up the catalyzer from the emulsin preparation, thus causing the latter to lose its effectiveness.

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**Chemistry of the Blackening of Carbohydrate Nutritive Mediums by *Bacillus Mesentericus*, Var. *Niger*.**

*Anna Muschel, Biochem. Ztschr., Berlin, 131:570, Sept. 16, 1922.*

*Bacillus mesentericus niger* grows on nutritive mediums to which there has been no addition of carbohydrates, of polyvalent alcohols or of amino-acids which are benzol derivatives, without essentially changing the color of the nutritive medium; but when it is grown on nutritive mediums to which sugar has been added (dextrose, mannose, galactose, levulose, lactobiose, saccharose, glycerin, dulcit, mannit, tyrosin), it colors the nutritive medium dark in its growth. This was observed for carbohydrates by Biel and Lunt. With the aid of albumin-free nutrient mediums it was shown that the black coloring is caused by bodies of the benzol series, which are closely related to the dioxybenzols (o-compounds and p-compounds) and are probably condensation products of these with amino-acids. This probably explains the color-deepening action of the amino-acids and amins when they act together with pyrocatechin and hydroquinon.

Attempts were made to prove this by adding different substances to the nutritive mediums and observing the hastening of pigment formation. Pyrocatechin was demonstrated as a transformation product of diluted, weakly alkalized sugar solutions; amino-acids or amins were found to strengthen the coloring action on the oxidation of very dilute solutions of pyrocatechin (demonstration of pyrocatechin and lactic acid in alkaline sugar solutions by Allain and Gaud, Nencki and Sieber, Gautier, and others). Chemically the process takes place as follows:

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In alkaline sugar solutions of 37° C., lactic acid can be split off from sugar by alkalis (Nencki and Sieber, Allain and Gaud, etc.). In addition to other organic acids, aromatic bodies are also formed (protocatechuic acid, Gautier, pyrocatechin, Allain and Gaud, dioxyphenylpropionic acid, Allain and Gaud). At high temperature or by strong alkalization the formation of dark products of oxidation can be brought about by the decomposition of the dioxybenzols that have been formed. At 37° C. and with moderate alkalization there is no spontaneous dark coloring. By the action of *Bacillus mesentericus*, var. *niger*, there is not a simple oxidation of the dioxybenzols, but the medium is changed in such a way that the blackening of the dioxybenzol is furthered. The neutralization of the alkaline sugar solution by the organic acids which are spontaneously split off is prevented by the fact that alkali is formed, so that the solution remains alkaline long enough; on the other hand, amins and amino-acids develop in the nutritive medium because of the powerful reducing action of the bacillus, which brings about the darkening of very dilute solutions of dioxybenzols, especially the p-compounds and o-compounds (formation of condensation products?).

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**The Inactivation of Saccharase by Iodin.**

*H. von Euler and Sture Landergren, Biochem. Ztschr., Berlin, 131:386, Sept. 16, 1922.*

Saccharase solutions are not very sensitive to molecular oxygen. On irradiation with sunlight as well as with ultraviolet light, inactivation of saccharase occurs if oxygen is present; in the absence of oxygen the inactivation is slight. Hydrogen peroxid only acts slightly on saccharase while ozone rapidly destroys it. The action of molecular iodine on saccharase was tested. The figures show that 0.32 mg. saccharase is weakened about 25% by approximately 0.03 mg. iodine. Amylase is also sensitive to iodine. Experiments have been made in isolating the iodized or oxidized and the noniodized constituents of saccharase and control experiments made as to toxicity, but the results are not reported.

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**Lactic Acid Fermentation of Glucose by Peptone.**

*Gottfried Schlatter, Biochem. Ztschr., Berlin, 131:362, Sept. 16, 1922.*

Bauer and Herzfeld showed that in sugar-peptone solutions sugar fermentation occurs which is called fermentation without yeast. This yields lactic acid for the most part, with a small amount of an iodoform-producing substance, probably alcohol. Experiments were planned to bring about quantitative fermentation of the grape sugar into lactic acid. It was found that an increasing concentration of bicarbonate decreased the degree of transformation; 1% bicarbonate was about the optimum, with 1% peptone and 1% sugar. Glucose in solutions which contained bicarbonate as a buffer were changed quantitatively into lactic acid by peptone at 37°. After a certain time the fermentation was at an end, indicated by a process of flocculation in the peptone. Peptone can

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ferment its own weight in sugar. The fermentation takes place more rapidly if more peptone is present. On the other hand, the concentration of the sugar has only a slight effect. Certain peptones have no fermentative action, including peptone Witte, Roche, and Merck sine sale, while peptone Siegfried, Merck e carne, and Merck ex albumine are active. The inactive peptones are practically free of phosphoric acid, while effectiveness of active peptones is clearly proportional to their phosphoric acid content. Phosphate-free peptones are not adapted for producing glucose-lactic acid fermentation. The peptone-sugar solution can be heated on a water bath before the addition of the buffer without injuring its fermentative power. During the fermentation and only then the number of free amino-acid groups in the peptone increases. Lactic acid bacteria cannot be demonstrated in the fermenting solution. Pure soluble amino-acids are ineffective. No colloid substances were found which in suitable solutions strengthened the action. All peptones contain tryptophan, demonstrable by red and violet stain with Rohde's reagent, which is made up of 20 gm. dimethylaminobenzaldehyd, 500 c.c. concentrated hydrochloric acid and 500 c.c. water. Tryptophan on any trace of putrefaction is changed into indol, recognizable by being stained red with a reagent consisting of 20 gm. dimethylaminobenzaldehyd and 500 c.c. water. The properly fermented solution on the addition of this reagent remains colorless, while with Rohde's reagent the unchanged tryptophan can be demonstrated.

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**Carbohydrates. II. A New Carbohydrate, 1,2-Anhydrid of Glucose.**

*Perey Brigl, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 245, Oct. 6, 1922.*

When a large excess of phosphorus pentachlorid acts on the  $\beta$ -form of pentacetyl glucose a strongly chlorinated product is formed by a complicated reaction, namely, 1-chloro-2-(trichloroacetyl)-3,5,6-triacetyl glucose, by replacement of the acetyl at carbon 1 by chlorin and of acetyl 2 by trichloroacetyl. In the replacement of the trichloroacetyl by chlorin in the triacetate of the 1,2-dichloroglucose, the chlorin atoms were in fact occupying the anticipated adjacent position. By the action of zinc dust, triacetylglucal was formed. The triacetyl could be detached from the molecule without disturbing the acid rests, by ethereal ammonia at  $0^{\circ}$ . The substance thus formed,  $C_{12}H_{17}O_8Cl$ , is closely related to the well-known acetochloroglucose but carries no acetyl at carbon 2 but a free hydroxyl group. It may therefore be designated as triacetochloroglucose. It contains 2 specially reactive adjacent parts, the hydroxyl and the chlorin. Moist silver carbonate acted on this by replacing chlorin by hydroxyl, while with zinc chlorid under the influence of heat hydrochloric acid was given off. For the action of ammonia the solvents of triacetochloroglucose must be perfectly anhydrous as otherwise at most complete saponification can be expected, but owing to the free hydroxyl groups of the glucose, solvents of the hydrocarbon type act very feebly. Acetone is a good solvent though no serviceable result was obtainable owing to the secondary reactions. But, with solution in benzene, solid, crystalline forms with melting point  $59.5^{\circ} C.$  were

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obtained on ammonia treatment. Only 1 molecule hydrochloric acid had been split, all acetyls remaining intact. This substance is to be regarded as the acetate of an anhydrid of glucose, namely, 3,5,6-triacetate of the glucose 1,2-anhydrid. It possesses high additive power and its ethylene oxid ring is split easily. Of additive reactions those with acetic anhydrid, with water and with methyl alcohol are specially noted. In the former, with brief heating, pentacetyl glucose is produced, with water 3,5,6-triacetate glucose, and with methyl alcohol triacetate  $\beta$ -methylglucosid.

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#### **Sugar Sulphuric Acids. IV.**

*Heins Ohle, Biochem. Ztschr., Berlin, 131:601, Sept. 16, 1922.*

By Neuberg and Samec agar was recognized as a carbohydrate sulphuric acid. The artificial preparation of such compounds is therefore desirable. Methods of preparing monosulphuric acid have been found by Neuberg and Liebermann. The determination of the constitution of these acids was attempted with glucose. The mixture of pyridin salts obtained after distillation of pyridin in a vacuum was acetylated with acetanhydrid and sodium acetate. A well crystallized sodium and pyridin salt of the completely acetylated glucose-monosulphuric acid could be prepared; this was saponified with baryta water. For comparison with this acetylated acid the readily accessible tetra-acetyl glucose was sulphonized and a second tetra-acetyl glucose-sulphuric acid obtained in the form of its sodium and pyridin salt. This differs from the preceding one, splits much easier and probably contains the  $\text{HSO}_3$  group in position 1. A pyridin salt of the second tetra-acetyl glucose-monosulphuric acid easily develops with acetobromoglucose in the presence of silver carbonate and has a melting point of  $143-144^\circ$ . In connection with the great mobility of the sulphuric acid ester it is probable that the preceding material justifies the conclusion that in the preparation of the acid from tetra-acetyl glucose no transformation has taken place, and that therefore it must be regarded as tetra-acetyl glucose-1-sulphuric acid. The compound obtained by direct sulphonization of the glucose is to be regarded as tetra-acetyl glucose-6-sulphuric acid. In the same way the sodium salt of triacetyl- $\beta$ -methyl glucosid-mono-sulphuric acid could be obtained. Similar experiments with galactose, fructose and saccharose were unsatisfactory.

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#### **The Salting Out of Polysaccharids and the Course of Acid Hydrolysis of Starch.**

*Hans Porger, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:92, Sept. 27, 1922.*

The method of salting out high molecular substances was applied to the decomposition of polysaccharids in order to isolate the different decomposition products. The amount of glucose formed in the indi-

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vidual stages was determined by means of a polarimeter. Hydrolysis took place with 2% hydrochloric acid. Magnesium sulphate proved a better precipitant than ammonium sulphate, sodium sulphate, sodium acetate or zinc sulphate. The presence of magnesium sulphate delayed hydrolysis, the percentage salt content being thus determined. Magnesium sulphate was employed in concentrations of 0.25, 0.5 and 1.0%, the hydrolysis requiring  $\frac{1}{2}$  and 1 hour. After hydrolysis for  $\frac{1}{2}$  hour with 1% hydrochloric acid, the hydrolyzed mixture no longer contained substances which could be salted out with magnesium sulphate, although there were still substances possessing high optical rotatory capacity. Thus, only the high molecular decomposition products were precipitated by magnesium sulphate. The starch molecule does not first disintegrate into two equal molecules of a high molecular substance, and these into further decomposition products in accordance with the same scheme. Nor is glucose derived immediately by cleavage of the starch molecule with the production of a smaller molecule which becomes continuously smaller with repeated cleavage of the glucose molecule. On the contrary, several unlike substances are formed with different high molecular weights, some higher, some lower. In this process probably no glucose is formed at first, but at most maltose. These higher molecular substances then decompose on their part into several substances of dissimilar molecular weights and so on, until glucose also appears. With continued decrease in molecular weight, the capability of cleavage by acid hydrolysis is increased.

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(1b—202)

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### **On Oxidation of Tertiary Hydrocarbons.**

*P. A. Levene and F. A. Taylor, J. Biol. Chem., 54: 351, Oct., 1922.*

This communication contains a report on the synthesis of 5 tertiary hydrocarbons, viz. (a) 3-methyl-heptane; (b) 3-methyl-nonane; (c) 5-methyl-nonane; (d) 5-propyl-nonane; (e) 5-methyl-dodecane. The method of preparation was the same as that employed by Levene and Cretcher in a previous work, namely, through the malonic ester synthesis. This tedious method was adopted because paraffins are freed from impurities with great difficulty and therefore can best be obtained in a sufficient degree of purity by a set of reactions, each simple in nature, and in which each intermediary substance can be isolated and purified. Concerning the oxidation by means of permanganate solution, it was found that for 5-methyl-nonane the conditions employed by Levene and Cretcher were the most favorable. The higher tertiary hydrocarbons, however, were not oxidized under identical conditions. This failure the authors think may be due to the lowering in solubility of the hydrocarbons with increase of their molecular weights. The conditions for the oxidation of substances with higher molecular weights have yet to be worked out. Among the acids formed on oxidation of 5-methyl-nonane, 2 were identified: acetic and butyric acids. The presence of some formic acid was detected.

The article contains detailed graphic, tabular and computational data that serve to outline the various steps.

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(1b—203)

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**The Amount of Histidin, Arginin and Lysin in the Proteins of the Crystalline Lens.**

*A. Jess, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 160, Oct. 6, 1922.*

Histidin and arginin were separated in the form of silver compounds from the hydrolysate that had been freed from humin and ammonia, whereupon lysin was precipitated with phosphotungstic acid. Two portions of crystallin were worked up consecutively, the results agreeing very satisfactorily. In  $\beta$ -crystallin the same amount of arginin (7.5%) was found as in  $\alpha$ -crystallin, a little less histidin (2.63% against 3.63%) and a little more lysin (4.6% against 3.75%). But the arginin content of the albumoid was rather higher (10.26%); histidin was somewhat less (2.74%), lysin the same as in  $\alpha$ -crystallin. In both crystallins, histidin was identified as monohydrochlorid, in the albumoid as picrolonate. Hitherto the 2 crystallins of the lens were classed with the globulins although they are water-soluble, the albumoid was classed with proteinoids or structural albumins. The former belong more properly to the albumins, as they possess 15% of the 3 stated building stones (hence 85% monamino-acids), no glycocoll and are water-soluble. The water-insoluble albumoid would represent a transition to the globulins in spite of lack of glycocoll. It has nothing in common with the albuminoids, which consist almost entirely of monamino-acids (elastin, keratin, reticulin) and are very rich in glycocoll.

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(1b—204)

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**The Chemistry of the Lungs. II. A New Phosphosulphatid in the Lungs.**

*Ubaldo Sammartino, Biochem. Ztschr., Berlin, 131: 411, Sept. 16, 1922.*

Acid combinations were found in the brain, as constituents of the white matter, which gave barium salts insoluble in both water and alcohol, and some of which contained phosphorus as well as sulphur and were therefore to be regarded as phosphosulphatids. In examining the lipoids of the lungs phosphosulphatids were also found which contained beautifully crystallized phosphorus, sulphur and nitrogen in the proportion of 1:1:2, showed no acid characteristics, and were distinguished therefore from the brain acids both by their nitrogen content and by their lack of salt-combining characteristics. Analysis showed it was an anhydrid of a phosphosulphatid, as this body gave no compounds with lead. It gave no orcin reaction, was free of galactosids, the solution showed no reaction to litmus, and the substance was completely free of lead. A hydrolysis was not undertaken on account of a lack of material.

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(1b—205)

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**On the Proteolytic Enzymes of the Spleen.**

*S. G. Hedin, J. Biol. Chem., 54: 177, Oct., 1922.*

To facilitate separation of the different enzymes the author mixed 100 gm. minced (ox) spleen with 300 gm. water and 2.25 c.c. 20%

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acetic acid. Chloroform and toluene were added to prevent bacterial action. After about 24 hours at 37° the contents of the bottle were filtered, filtrate A being kept for subsequent investigation, while the residue was thoroughly washed with water and mixed with 150 c.c. casein solution, obtained by dissolving 20 gm. casein in 400 c.c. water plus 100 c.c. 0.1 n. NaOH. Chloroform and toluene were again added and the whole digested for 24 hours at 37° C. and then filtered, filtrate B being set aside for study. The residue was thoroughly washed and then extracted with 5% NaCl solution at 37° C. for 24 hours, the solution filtered off and 30 gm.  $\text{Am}_2\text{SO}_4$  added to each 100 c.c. solution. The precipitate formed on the addition of the salt was filtered off and dialyzed after the addition of water. When the  $\text{Am}_2\text{SO}_4$  had been nearly completely removed, the fluid was filtered from the undissolved proteins, the residue on the filter dissolved in as little NaOH as possible, forming after filtration solution C.

In studying the action of the filtrates A, B, and C on solutions of casein and of Witte's peptone in media of varying pH, it was found that extracts of the minced, acidified (ox) spleen contain at least 3 different enzymes: (1) a-protease, acting upon the spleen substance and upon casein in an alkaline medium (pH 8.8); (2) b-protease acting upon the spleen substance and upon casein in a weakly acid medium (pH about 5.4); and (3) erepsin, not acting upon casein but having its most powerful action upon Witte's peptone at pH 7.5 to 8.5. A watery extract of the spleen, obtained at about pH 5.2, contains varying quantities of all the enzymes referred to.

Regarding the distribution of the particular enzymes in the respective filtrates, it was found that after minced ox spleen is digested with acetic acid filtrate A contains all enzymes; residue is extracted with casein solution, becoming filtrate B which contains mainly b-protease and erepsin; residue is extracted with NaCl solution, becoming filtrate C which contains mainly a-protease. In general, the spleen of the horse gives the same results. The most important difference between the spleen of the pig and that of the ox is that the amount of acid used for the original treatment of the spleen mass should not exceed 1 c.c. 20% acetic acid to 100 gm. spleen and 300 c.c. water. More acid seems to be somewhat injurious to the enzymes.

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(1b—206)

#### Proteolytic Enzymes of the Kidneys.

*S. G. Hedin, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 307, Oct. 6, 1922.*

(1b—206)

Proteolytic enzymes found in the horse's kidney are (1) an erepsin which acts best on peptone in an alkaline reaction,  $\text{pH} = 7.8$ ; (2) an enzyme acting best on the organ's albuminous substances and on casein in a feeble acid reaction,  $\text{pH} = 4.3-5.6$ . No conversion takes place at the hydrogen-ion concentration most favorable for pepsin action. No enzyme could be found that acts best on the organ's albumin or on casein in an alkaline reaction. If such is present it can only be very feeble. When the whole fresh kidney is kept at a weak alkaline or very weak acid reaction the enzymes largely lose their activity permanently. That is preventable by immediate addition of acid. Bradley's

results in the matter of proteolytic enzymes in ox kidney are in agreement with the foregoing.

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(1b—207)

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**Chemistry of the Reaction of Rivalta in Exudates.**

*F. Alzona, Policlinico (Pract. Sect.), Rome, 29:1353, Oct. 16, 1922.*

From many organs it is possible to isolate substances which, in a weakly acid medium, have the property of precipitating albumins with which they come in contact. A group of similar substances, typified by sulphochondroitinic acid, have been isolated from various organs by the present author. These substances, which the author was able to obtain by a special technic in phosphorus-free form, possess the property of precipitating in acid mediums both albumin and gelatin; they decompose after exposure to heat or to strong acids; in sulphuric acid they act like strongly reducing substances; and they are precipitated out of their own solutions by the addition of alcohol or acetic acid in excess. By means of an original method the author has succeeded in isolating from the precipitate obtained in rivalta's reaction a nonprotein substance, white or dirty white in color, existing in minute quantity even in voluminous masses of exudate. This substance shares many of the properties of chondroitinic acid: both precipitate albumin in slightly acidified mediums, and both contain a fraction which reduces Fehling's solution after previous boiling in concentrated hydrochloric acid. The substance described differs from chondroitinic acid in that it has not been shown to contain a sulphuric acid nucleus chemically united to the remainder of the molecule, and does not precipitate gelatin in solution.

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**The Nature of Ehrlich's Diazo-Reaction. III.**

*Leo Herrmanns, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:98, Sept. 16, 1922.*

It has been confirmed that the protein split-products on which the positive diazo-reaction in tuberculosis depends must be phenols and that these occur in the patient's urine in the form of alkylsulphuric acids. After incomplete cleavage of urinary ethereal acids 2 different pigments are obtained on coupling. They are prepared by boiling 10 liters of fresh tuberculous urine 5 minutes over wire netting. Following coupling with dichlorodiazobenzene in alkaline (soda) solution the precipitated pigment is collected on a filter and washed thoroughly with water. The air-dried red pigment is extracted with ether in the Soxhlet apparatus. The residue is insoluble in ether, soluble in dilute alcohol. During hydrolysis, sulphuric acid is split off. The alkylsulphuric acids are prepared by Baumann's method from tuberculous urine, converted into potassium salts and heated an hour at 180° in a nickel crucible with 25 gm. concentrated caustic potash and 5 c.c. water. The fused mass gives a splendid diazo-reaction. The constitution of the substance is determined by analysis. The pigment's melting point is 68-70°. It is free from sulphur, dissolves in pyridin with a deep red color and is

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insoluble in water and petroleum ether. On keeping in the desiccator coarse, dark red, irregular prisms are formed. Micro-analysis yields the formula  $C_8H_6O_4$ . The substance is free from nitrogen and is surely a polyvalent phenol corresponding to the high oxygen content. Probably it is a compound of a benzene ring with an unsaturated ring, a coumarin oxidized in the benzene nucleus. Engeland pointed to the occurrence of histidin in normal urine. The coupled products of dichlorodiazobenzene with histidin and benzene-histidin are intense red pigments behaving like indicators. The imidazol ring of histidin binds two azo rests, diazobenzoylhistidin being formed. On boiling with glacial acetic acid the pigment's acid is obtained as yellow, small crystalline needles. The author was unable to find a pigment in the urine possessing the aforesaid properties. Ehrlich's reaction was also demonstrated in urine of typhoid patients by coupling, both in the distillate and in the small needles obtained by further treatment. The reaction depends on the precipitation of phenol-like metabolic products and is to be regarded as the expression of toxic albumin disintegration.

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(1b—209)

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**A Urea Reaction with p-Dimethylamidobenzaldehyd. I.**

*H. K. Barrenscheen and O. Weltmann, Biochem. Ztschr., Berlin, 131: 591, Sept. 16, 1922.*

Meyer-Estorf describes a green benzaldehyd reaction in icteric urine. It was a nitrite-containing urine. The hydrochloric acid of the aldehyd reagent formed free  $HNO_2$ , which caused the oxidation of the bilirubin and biliverdin. Greatly diluted normal urine gives with Ehrlich's aldehyd reagent (p-dimethylamidobenzaldehyd in acid solution) an intense green color which increases on standing. It was found in the examinations that the green color was caused by urea. Aside from allantoin no other constituent of the urine shows the reaction. The presence of free hydrogen ions is necessary to the development of the reaction. The acid ion has no effect. Attempts were made to demonstrate urea in the serum in this way and it was found that in serum dealbuminized with trichloracetic acid the reaction appears with a residual nitrogen content that exceeds 36-46 mg. per hundred; it can therefore be used simply as a qualitative demonstration of increased residual nitrogen. The residual nitrogen was determined by Pregl's microkjeldahl method, using 2 c.c. of the filtrate of the trichloracetic acid precipitation, corresponding to 1 c.c. serum.

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(1b—210)

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**Comparative Dialytic Diffusibility of Urea, Sodium Chlorid, Uric Acid and Glucose.**

*A. Chauffard, P. Brodin and A. Grigaut, Ann. de méd., Paris, 12: 257, Oct., 1922.*

In these experiments uric acid was used in the soluble form found in the organism, i.e. as sodium urate. The authors first repeated Graham's fundamental experiments: 1 gm. of the various substances dissolved in 100 c.c. water was placed in a parchment dialyzer having

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an area of 1 sq. decimeter, the external water being constantly changed and maintained at a temperature of 15° C. The amount of dialyzed substance was calculated at the end of 24 hours, and if the diffusion power of sodium chlorid is taken as 1, that of urea was found to be 1.04; of sodium urate, 0.77 and of glucose, 0.62. In a second series of experiments, 100 c.c. of a 0.05 n. solution of the various substances were placed in the dialyzer. Under the same conditions as before it was ascertained that the proportion of these equimolecular quantities which was dialyzed at the end of 24 hours was for urea, 93%; sodium chlorid, 92%; sodium urate, 74%; and glucose 59%. Other experiments were made with blood serum, urine and artificial solutions containing the same quantities of urea and sodium urate as are normally contained in these fluids; 200 c.c. of the fluid to be examined were placed in the dialyzer, and 200 c.c. distilled water in the outside container, the contents of which were not changed. Tests were made at regular intervals to ascertain the degree of dialysis that had taken place, until equilibrium was reached between the 2 solutions, the results being expressed by curves. Dialysis was found to be slower for urine than for the other fluids investigated, and in all urea diffused faster than sodium urate.

These results throw some light on certain biologic facts. Urea and sodium chlorid, for instance, are found in the same concentrations in the cerebrospinal fluid and in the serum, this being in accord with their experimental diffusion coefficient which is close to 100%. Likewise the concentration of glucose in the spinal fluid which is less than half of its concentration in the blood, roughly corresponds to its coefficient of diffusion (59%). It seems, therefore, that the composition of the spinal fluid as regards the above substances is determined rather by dialysis than by a purely selective secretion. As only traces of uric acid, on the other hand, pass into the spinal fluid, it may be supposed that the living meningeal membranes exercise a negative selective action against this substance. This property is not possessed by the pleural and peritoneal membranes, for uric acid is found in proportions equivalent to those of the serum in pleuritic and ascitic fluids. Although the importance of dialytic diffusion should not be exaggerated, it probably plays a considerable rôle in many pathologic conditions, for instance in the impregnation of the tissues by glucose and uric acid in diabetes and gout.

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(1b—211)

#### **Pyrrols and Oxypyrrols.**

*Hans Fischer and Marianne Hermann, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 1, Sept. 16, 1922.*

Bilirubinic acid is composed of an oxypyrrol and a pyrrocarboxylic acid. Pyrrol-1 yields a finely crystallizing diacetyl compound. When pyrrol-1 was dissolved in glacial acetic acid and a concentrated solution of sodium nitrite was added slowly under cooling a reddish brown solution was obtained from which the nitrous compound has not been isolated so far. Pyrrol-3 was condensed to a finely crystallizing pigment with dimethylaminobenzaldehyd, which is characterized by a splendidly colored hydrochlorid. Oxypyrrol (3 gm.) was

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heated with benzaldehyd (6 gm.), a knife-point of potassium bisulphate being added as condensing agent to the hot solution, which assumed a reddish brown color. The whole solidified to a yellow mass. Recrystallized from alcohol it yielded fine, lustrous yellow needles, with melting point of  $228^{\circ}$ . With Ehrlich's reagent a red color was produced, also momentarily with iron chlorid. The substance was easily soluble in glacial acetic acid, alcohol and pyridin, slightly in chloroform, very slightly in ether, ligroin and acetone, and insoluble in water. Next, 3 gm. oxypyrrol was dissolved in boiling alcohol, 2 gm. alcoholic dimethylaminobenzaldehyd added with a knife-point of potassium bisulphate. A dark red and brown color appeared immediately. Boiling was continued 2 minutes longer and  $\text{KHSO}_4$  then filtered off. One-third of the volume of boiling water was then added. On cooling ochre-yellow needles separated, with melting point of  $214^{\circ}$ . Iron chlorid produced a momentary bluish red color. From the acetone solution an immediate dark precipitate of small, almost black needles was obtained; in alcohol and acetone this dissolved easily, but in chloroform and ether with difficulty. The needles from alkaline solution were readily soluble in water. On combining oxypyrrol with formaldehyd and hydrochloric acid no condensation occurred, which, however, took place with formic and hydrocyanic acids. Oxypyrrol was also dissolved at the boiling point with acetic anhydrid, removed quickly from the flame and a knife-point of sodium acetate added to the brown solution which turned only slightly darker. When the reaction had taken place the solution was again boiled twice and then allowed to cool. Small yellow needles gradually appeared. By cautious addition of more water the acetyl product was precipitated almost quantitatively in the form of small, faintly colored, fine needles. The precipitate was filtered off, dissolved in alcohol, treated with animal charcoal, boiled 5 minutes and filtered. The precipitate, when recrystallized from alcohol, yielded pure white needles with melting point  $123^{\circ}$  C. With Ehrlich's reagent a green color was obtained. The cold substance was readily soluble in glacial acetic acid, chloroform, acetone and pyridin. It was insoluble in water and ether. Finally, oxypyrrol was suspended in pyridin, benzoyl chlorid being added gradually during constant shaking until a congo-acid reaction took place. The pyrrol went into solution, the latter assumed an intense red and reddish brown color and pyridin hydrochlorid was gradually precipitated. After shaking 2 hours the whole solution was poured into ice cold dilute sulphuric acid whereupon the benzoyl product separated as a red oil. By kneading and rubbing, a more brightly colored product having a pasty consistency was finally obtained from the oil. As it adhered to the glass rod it was removed and recrystallized several times from alcohol but always came out viscous. Only once 3 very large rhombohedral colorless crystals formed. The melting point was  $127^{\circ}$  C.

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**The So-Called Benzaldehyd Reaction in Bilirubin Urine.**

*K. Hoesch, Klin. Wchnschr., Berlin, 1:2034, Oct. 7, 1922.*

In certain forms of icterus the urine turns green on the addition of Ehrlich's reagent; this reaction appears also in the bilirubin-free filtrate

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of the urine. Also a urea solution alone reacts in the same way with the Ehrlich reagent. But this reaction is covered in the urine by normal or pathologic urinary pigments and appears only in clear or filtrated urines. Completely different from this urea reaction is the green coloring which urines containing bilirubin show after the addition of Ehrlich's reagent. The color tone is much stronger and more bluish. This reaction, however, is not caused by the aldehyd but by the acid component of the reagent. All acids give this reaction, but the simultaneous urea-aldehyd reaction is concealed and appears only in the charcoal filtrate, and then, indeed, alone. The irregular appearance of the green coloring in bilirubin urine on the addition of acid shows the presence of an oxidizing substance. The author found this to be a nitrite.

The similarity of the color reaction with Gmelin's test and the prompt appearance of the same green coloring on the addition of a nitrite support this assumption; in none of the urines which did not give a green reaction could nitrite be demonstrated. Also the time of the reaction and the outcome of the nitrite reaction and the green coloring, which run parallel, indicate the correctness of this connection. Traces of nitrite change urobilinogen immediately into urobilin; in a urine containing an abundance of urobilinogen and little bilirubin, if nitrite is formed by bacteria or is added to the urine, then in place of the red aldehyd reaction the oxidation reaction appears. In freshly discharged urine the reaction may appear seldom, but from this the conclusion cannot be drawn that urobilinogen is lacking and that for instance there is an occlusion of the common duct; only the urobilinogen reaction can decide that. The acid nitrite test is of equal value with Ehrlich's diazo test in the demonstration of bilirubin; an excess of nitrite and acid must be present; also lead peroxid and iodin in acid solution act in the same way. Rosenbach's test, however, is more sensitive, while the most sensitive test of all is that of Nakajama. The green reaction of bilirubin urine is an acid nitrite reaction and is caused by oxidation to biliverdin.

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#### Method of Demonstration of Urobilinogen.

*E. Herzfeld, Schweiz. med. Wchnschr., Basel, 52:976, Oct. 5, 1922.*

Freshly discharged feces are weighed and rubbed up into a homogeneous pulp. Five grams are placed on a weighed watch glass for dry substance determination and 1.25 gm. rubbed up in a mortar with 10 c.c. of a saturated alcoholic zinc acetate solution, filtered, washed with small portions of the zinc acetate solution and finally filled up to 30 c.c. It is well mixed and after standing 24 hours a series of dilutions are made and the limit of fluorescin reaction determined. If starting from the zinc acetate solution it is found that 10 tubes show the reaction before the limit of reaction is reached, this indicates 0.5 mg. urobilin to 1 c.c. and 15 mg. to 30 c.c. of the zinc acetate solution, or to the 1.25 gm. of native feces. By simple calculation the total amount of urobilin is found for the whole 24 hours' amount of native or dried feces. If in the fresh feces there were less urobilin and more urobilinogen, the urobilin determinations would give different values. But in the experi-

ment under consideration this was not the case; the fresh feces kept 23 hours in a vacuum and in a moist chamber, also feces slightly oxidized with hydrogen peroxid showed exactly the same results; the fluorescent fluids gradually increased in intensity and after 24 hours were completely identical. The gradual increase in the fluorescein reaction, therefore, cannot be regarded as a proof of the existence of a preliminary stage of urobilin, but it corresponds to a reaction time which is necessary to attain the optimum of fluorescence under the given conditions.

The author has made similar experiments with normal and pathologic urines, and confirmed the findings of H. Fischer and D. Meyer, according to which with bicarbonate alkaline reaction a crystalline body, similar to hemibilirubin urobilinogen, can be isolated from the urine with chloroform. The existence of urobilinogen as a constant precursor of urobilin may be doubted. The very slight amounts of urobilinogen in the urine can rather be regarded as a further reduction product, which probably arises in the transformation of blood urobilin into urine urobilin by the kidney. From his experiments, the author comes to the conclusion that there is no urobilinogen in the feces.

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**A Method for the Microdetermination of Chlorin in the Blood and Other Mediums Containing Albumin.**

*M. Claudius, Ugeskr. f. Laeger, Copenhagen, 84:1366, Oct. 12, 1922.*

The method devised by the late Ivar Bang for quantitative determination of chlorin in the blood is imperfect, and Claudius has devised a method which takes only  $\frac{1}{4}$  hour without complicated apparatus. Into a capillary pipet, such as is used for hemoglobin tests, 20 c. mm. of blood is drawn from the ear. The pipet is emptied into a test-tube of Jena glass containing a few drops of water, and is then washed out with a few drops of water into another test-tube, the contents of which are added to the first test-tube. With a pipet (graduated to 0.01 c.c. and having a capillary point), 0.2 c.c. of 0.04 n.  $\text{AgNO}_3$  solution containing a trace of  $\text{HNO}_3$  is added to the test-tube. Then 4-5 drops of pure concentrated  $\text{HNO}_3$  are added and the mixture is heated, but not allowed to boil, until the coagula are dissolved. Then the solution is boiled over a flame and the test-tube is constantly shaken until the solution has become quite clear except for a trace of silver chlorid. The heating is continued until approximately the volume of added  $\text{HNO}_3$  has been evaporated. One drop of 4% solution  $\text{KMnO}_4$  is added, dispelling the yellow color. After thorough cooling, about 5 c.c. of pure absolute alcohol and 1 drop of 4% solution of nitrate of iron, faintly acidified with  $\text{HNO}_3$ , are added. From the microburet is now added 0.5 c.c. of 0.005 n. potassium thiocyanate in absolute alcohol. After shaking, the mixture is poured in approximately equal portions into 2 small flasks. To the one, there is added drop by drop the KCNS solution from the microburet, the flask being constantly shaken. This is continued until the color change just differs from that in the second flask, becoming a faint rose. As soon as this has been attained, the contents of the second flask are titrated until the colors are identical. The quantity of KCNS used is subtracted from the quantity of  $\text{AgNO}_3$  solution (calculated at



0.005 n.), and the resulting figure ( $d$ ) of 0.005 n.  $\text{AgNO}_3$  shows the amount of chlorin present in the blood. Based on titration with 0.005 n. solution and using 20 c. mm. blood, the NaCl percentage would be  $(d \div 2) (58.5 \div 20)$ , which can be expressed in the general formula:  $(d \div 2) (58.5 \div a)$ ,  $a$  being the amount of blood in cubic millimeters.

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**A Method for the Purification of Picric Acid for Creatinin Determinations.**

*Stanley R. Benedict, J. Biol. Chem., 54:239, Oct., 1922.*

Existing methods dealing with the purification of picric acid for creatinin determination proving so unsatisfactory, Benedict set about devising a new method. He found that a single crystallization from benzene resulted in obtaining an excellent picric acid from the very worst commercial sample. Procedure: In a 2 liter flask is placed 400 gm. moist picric acid, to which 1 liter of pure benzene is added. The mixture is heated to vigorous boiling on an electric plate. Soon after the boiling point is reached the picric acid practically wholly dissolves, leaving a residue of dirt and foreign material, together with the water, which settles quickly to the bottom when the mixture is not boiling. The hot mixture is poured upon a large fluted filter which has been previously moistened with benzene, the solution being poured slowly enough so that most of the foreign sediment, together with the water, remains in the flask. This material (about 50 c.c. in volume) should be discarded, and not poured upon the filter. The clear filtrate should be received in a beaker of about 2 liters capacity and when the filtration is completed the beaker is covered with a large watch-glass, and heated on the electric plate until the picric acid which has begun to crystallize is again brought into solution. The covered beaker is allowed to stand over night without agitation when the picric acid will be found to have crystallized on the bottom and sides of the beaker in large, hard, yellow-brown crystals, from which the excess of benzene can readily be drained without recourse to any filtration. The crystalline mass is washed twice by gentle rotary shaking with 75 c.c. portions of benzene, and the residue finally allowed to drain thoroughly for 15-30 minutes. The crystallized picric acid can now be freed from the last of the benzene by placing in an air bath at about  $80^\circ$  for a few hours, with occasional stirring. The product should be finally powdered by gentle rubbing in a mortar, and preserved in a brown glass-stoppered bottle. About 85% of the picric acid used is recovered in the purified form. The benzene may be recovered by distillation, preferably in vacuo from a water-bath.

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**Picric Acid Compounds (Uripicrate).**

*Peter Bergell, Ztschr. f. klin. Med., Berlin, 95:63, Sept. 15, 1922.*

On 1:5 saturation of the urine with sodium chlorid and the addition of Esbach's citric acid reagent a crystalline precipitate forms. This is a compound of 1 molecule picric acid with 1 molecule uric acid. On treating the precipitate with an alcoholic solution of hydrochloric acid,

pure uric acid and a compound of picric acid uric acid are obtained. From a solution of organic bases of uric acid, picric acid precipitates a compound of uric acid and picric acid bases. This is less soluble in water and salt solution than the uric acid base alone. Such compounds the author calls uripicrates and he examined the following ones: ethyl-endiaminuripicrate, pentamethylendiaminuripicrate, piperazinuripicrate, piperidinuripicrate. These compounds are treated with alcoholic solution of hydrochloric acid, filtered off from the precipitated uric acid base, the alcohol driven off, the residue etherized, and the free base identified with the  $\beta$ -naphthalinsulphochlorid reaction. Probably the crystalline nephritic picrates are analogous uripicrates (of the type of the diamins or heterocyclic bases).

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**The Colorimetric Estimation of Cystin in Urine.**

*Joseph M. Looney, J. Biol. Chem., 54:171, Oct., 1922.*

The author's recently described method for the colorimetric estimation of cystin is herewith applied to the quantitative determination of cystin in urine. The process depends on the fact that cystin reacts with phosphotungstic acid in the presence of sodium sulphite to give a deep blue color. Cystin alone, without the addition of sodium sulphite, does not give any color with the reagent. Uric acid and the other urinary constituents which reduce phosphotungstic acid, under certain conditions give the same color whether sodium sulphite is present or not. The amount of cystin in urine is estimated by determining the increase in color of the specimen after the addition of sodium sulphite. The fact that the addition of sulphite does not alter the depth of color produced by uric acid contained in urine allows one to use a solution of cystin as the standard, and to determine the cystin content by subtracting the cystin equivalent of the urine before the addition of sulphite from that obtained after such addition.

Procedure: The standard consists of a solution of pure cystin in 5% sulphuric acid made up to contain 2 mg. cystin to 1 c.c. solution. For each determination 1 c.c. of the standard is taken. Of this standard solution 1 c.c. is placed in a 100 c.c. volumetric flask, and 20 c.c. saturated sodium carbonate, 10 c.c. 20% sodium sulphite, and 1 c.c. 20% lithium sulphate are added and the solution is well mixed. In a second flask 1-10 c.c. (usually 2 c.c.) urine is placed and treated in a similar manner. In a third flask the same amount of urine is placed and treated as above except that no sulphite is added. Then 3 c.c. uric acid reagent of Folin and Denis is added to each flask and the flasks well shaken. After standing 5 minutes the solutions are diluted to volume and mixed. The solutions are read against the standard set at 20.0. The time of reading must not be later than 8 minutes after the reagent is added and for this reason a new standard must be prepared for each determination. The amount of cystin is found by subtracting the amount of reducing substances in the third flask, calculated in milligrams of cystin, from the total color-producing substances after the addition of sulphite, found in the second flask, also calculated in milligrams cystin. In cases in which there is much cystin it is necessary to use a different amount of urine for the blank and total color readings so the latter will come between the usual limits of 13.0 and

27.0. It is then necessary to reduce both amounts to the same quantity before subtracting. When the urine is so concentrated that cystin is precipitated, dissolve the centrifuged precipitate in a small amount of 5% sulphuric acid and dilute to a definite volume. The 2 solutions are determined separately and the amounts combined to give total quantity. If the urine contains albumin it must be removed before attempting to estimate the cystin.

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**The Estimation of Formic Acid in the Urine.**

*Ethel M. Benedict and G. A. Harrop, J. Biol. Chem., 54:443, Oct., 1922.*

During the course of clinical and experimental studies of acute methyl alcohol poisoning the authors devised the following procedure for the quantitative estimation of formic acid in the urine: Into a liter volumetric flask containing 500-600 c.c. water, 100 c.c. urine is accurately measured. Then 100 c.c. 20%  $\text{CuSO}_4$  is added and the whole well mixed. A 10% suspension of  $\text{Ca}(\text{OH}_2)$  is now added until alkalinity, as evidenced by the characteristic color change from green to blue, occurs. The contents are made up to volume and mixed. After standing 15-30 minutes they are filtered and a 600 c.c. aliquot is placed in an 800 c.c. Kjeldahl flask, with 2-3 drops of phenolphthalein as an indicator, and made distinctly acid with 85% phosphoric acid. Sufficient excess should be added to free all of the formic acid present (1-2 c.c. is ample for this purpose). Glass beads are added to prevent bumping. This flask is connected with a supply of steam and with a water condenser by means of a Kjeldahl trap, the neck of the flask and the outside of the trap being well wrapped with asbestos cord to prevent loss of heat. The distillate is caught in a casserole provided with 15-20 c.c. 0.1 n.  $\text{NaOH}$ , and a few drops of phenolphthalein are added to make sure that it is alkaline. This alkalinity must be maintained throughout the distillation by the addition of further 0.1 n.  $\text{NaOH}$  as may be necessary, but a great excess must be avoided. The distillation must be so managed that at first a slow stream of steam is conducted in, while the contents of the distilling flask are rapidly driven over by brisk heating and reduced in volume to 50-75 c.c.

At this amount they must remain until 2 liters are collected. The distillate is then evaporated to dryness over night on the water-bath, and the residue taken up in exactly 100 c.c. distilled water and filtered. A 90 c.c. aliquot is placed in a 250 c.c. Erlenmeyer flask and made just acid with 0.1 n.  $\text{HCl}$ . Then 10 c.c. of a special  $\text{HgCl}_2$  mixture (which contains 200 gm.  $\text{HgCl}_2$ , 80 gm.  $\text{NaCl}$ , and 300 gm.  $\text{Na}$  acetate to 1 liter of water) is added, the flask fitted with an air condenser and heated in a boiling water-bath for 1 hour. After cooling the mercurous chlorid is filtered into a weighed Gooch crucible, washed with 100 c.c. 5% cold  $\text{HCl}$ , then water, alcohol, and ether, and dried 1 hour at  $105^\circ$  and weighed. The blank of the reagents in the authors' experiments varied from 0.0014 to 0.0044 gm. according to the reagent used. The amount of formic acid per liter in the original urine is then  $1.01 \times \frac{10}{6} \times \frac{10}{9} \times 0.0975 \times (\text{weight of precipitate—weight of blank of reagents})$ . One gram of  $\text{HgCl}$  equals 0.0975 gm. formic acid.

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**The Quantitative Determination of Glucose and Lactose in Blood and Urine.**

*William Thalhimer and Margaret C. Perry, J. A. M. A., 79:1506, Oct. 28, 1922.*

The principle on which the authors' method is based is that of the selective destructive action of various bacteria on different sugars. The total amount of sugar present in a specimen is first determined as glucose; the Folin-Wu blood sugar method is used for blood or serous fluids; the recent method of Folin and Berglund for sugar in normal urine is used for urine specimens. The material is then heavily inoculated with *Bacillus paratyphosus B*, from a 24 hour growth on an agar slant, and is inoculated for 48 hours. The amount of sugar remaining is then determined by the appropriate method. If no reducing substance is left, only glucose is present; if there is still a reducing substance, this is determined as lactose. Since the sugar-splitting ability of *B. paratyphosus B* is limited, preliminary sugar determinations of an unknown solution should be made; and, if necessary, the concentration of glucose or of lactose should be reduced, before inoculation, to about 0.3%.

**1c. PHARMACOLOGY AND TOXICOLOGY**

**PHARMACOLOGY**

(1c—162)

(1c—162)

**The Pharmacology of Potassium and Calcium Ions.**

*Max Rosenmann, Klin. Wchnschr., Berlin, 1:2093, Oct. 14, 1922.*

The author investigated the action of potassium and calcium ions on the excised intestine of the rat and *Rana esculenta* and other non-striated muscular organs in a nutrient solution free from potassium, or calcium, or both. These experiments show that both potassium and calcium act in a different manner (diametrically opposite) below their physiologic concentration than they do above it; that potassium exercises chiefly an inhibitory, and calcium chiefly a stimulating, influence. Probably the inhibitory action is equilibrated at a certain relative concentration of both salts in the Ringer solution so that their stimulating action then begins. This is supported by the fact that the mode of action of these ions depends, within certain limits, not on their absolute concentration, but on their concentration relative to each other. The optimum condition for the stimulating potassium action commences approximately at physiologic concentration and rises to five times normal concentration. Above the latter concentration potassium induces first tetanus, then paralysis. The optimum condition for the stimulating calcium action increases up to physiologic calcium concentration; the tonus-inhibiting action commences soon after physiologic concentration, the rhythm being first accelerated and later inhibited with increasing calcium content. The direction of the action after increase of potassium or calcium depends on the slight fluctuations around the physiologic concentration. Precisely these slight fluctuations take place in the organism and may induce diametrically opposite results. Under both

physiologic and pathologic conditions, they are capable of influencing the individual cell and the relation between different cell groups in the most diversified manner.

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(1c—163)

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**The Action of Calabash Curare on Iris Movement.**

*Tomoichi Nakagawa, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196:123, Sept. 27, 1922.*

The mydriasis observable after curare poisoning in frogs and mammals with larger doses than are requisite for motor paralysis may set in also without a reaction and has not been explained so far. Neither indirect effects (oxygen insufficiency) nor vascular changes affecting the pupil can be involved. The pupillary innervation is therefore suggested as the point of attack. In experiments on 9 dogs and 5 cats, 1% curare solution being administered subcutaneously under artificial respiration, the ciliary ganglion, the short ciliary nerves and the oculomotor nerve were exposed by P. Schultz's method. Fairly large curare doses regularly produced mydriasis or miosis in Argyll-Robertson pupils. Such mydriatic eyes showed contraction of the pupil on stimulation of the short ciliary nerves, whereas only exceptionally strong stimuli acted on the oculomotor nerve, so that this action may possibly be referred to current leaks into the ciliary nerves. Stimulation of the cervical sympathetic induced immediate dilatation. Accordingly, the irritability of the postganglionic parasympathetic fibers was preserved, that of the preganglionic (oculomotor) fibers being abolished. Fairly large curare doses may be assumed to produce paresis either of the preganglionic fibers or of the ciliary ganglion. As local applications have the same action on the ciliary ganglion, followed by normal reactions after washing with sodium chlorid solution, the poison's point of attack must obviously be sought in the ganglion. The nonirritability of the oculomotor nerve in curare poisoning was observed in 1892 by Langley.

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(1c—164)

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**The Action of Pilocarpin and Atropin on Isolated Toad's Muscle and Its Dependence on the Ion Mixture.**

*O. Loewi and J. Solti, Klin. Wchnschr., Berlin, 1:2046, Oct. 7, 1922.*

Pilocarpin and atropin have a pronounced action in the same direction on the isolated sartorius of the toad, the former in a concentration of 1:2000, the latter at one of 1:20,000. The nature of the action is dependent on the ion mixture of the bath. In Ringer's solution the contraction is increased, in calcium-free solution in which the contraction is abnormally great and the fall very sluggish, the contractions become rapid under the influence of these toxins and their size decreases considerably; the addition of calcium brings them again to their original size. Though pronounced permeability changes take place in only one direction they do not entirely explain the phenomena observed. Other changes must be decisive for the action of pilocarpin and atropin. The same is true for the restorative action of calcium which considerably



increases the permeability for phosphoric acid. Sodium rhodanate inhibits permeability, sodium tartrate furthers it.

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(1c—165)

(1c—165)

**A Chemical Method of Assaying the Active Principles of Digitalis.**

*Arthur Knudson and Melvin Dresbach, J. Pharmacol. & Exper. Ther., 20:205, Oct., 1922.*

Tincture of digitalis 5 c.c. (or an equivalent amount of drug in the form of a fluid extract or infusion) is measured into a 25 c.c. volumetric flask and diluted with water to about 15 c.c. To this solution 2.5 c.c. lead acetate is added, contents mixed, and then diluted with water to the mark. After mixing thoroughly and allowing to stand a minute, the solution is filtered; 12.5 c.c. filtrate is then measured into another 25 c.c. volumetric flask and 1.25 c.c.  $\text{Na}_2\text{HPO}_4$  solution added in order to precipitate the excess lead. The contents of the flask are then diluted to the mark, mixed thoroughly, and filtered. The filtrate should be crystal clear but may have a slight tinge of yellow color. Transfer 5 c.c. filtrate to a 10 c.c. volumetric flask or tube graduated at 10 c.c. and at the same time transfer 5 c.c. standard ouabain solution to another volumetric flask. To both of these flasks add 5 c.c. alkaline picrate solution, mix, and allow to stand at least 20 minutes. Make comparisons in the colorimeter, setting the standard most conveniently at 20 mm. The color comparison should be read 20-35 minutes after the alkaline picrate has been added, so that it is never advisable to develop the color in more than 3-5 specimens at a time. Instead of using the standard ouabain solution, the permanent standard of potassium dichromate solution can be put in the colorimeter, set at 20 mm. and the unknown specimens compared after color has been allowed to develop in the manner described. The depth of the unknown (in millimeters) divided by the reading of the standard, and multiplied by 2 times the number of milligrams of drug in the aliquot portions of specimen tested, gives the number of milligrams of drug equivalent to a cat unit as expressed by the Hatcher and Brody method.

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(1c—166)

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**Experimental Study of the Vascular and Diuretic Effect of Small Doses of Digitalis in the Rabbit.**

*Lucien Beco and L. L. Plumier, J. de physiol. et de path. gén., Paris, 20:346, July-Sept., 1922.*

In the tests reported, the carotid pressure was measured by a mercury manometer and the urine allowed to escape, drop by drop as secreted, through a cannula placed in the urethra or bladder. Anesthesia was obtained usually by urethan, in some cases by ether, and one test was made without anesthesia. The test drugs—strophanthin, digalen, digitalin and theocin acetate—were injected into the veins of the ear. The kidney was left intact, no kidney tracing being made. The dosages ranged from 0.125 to 0.5 mg. of the first 3 drugs mentioned, the dose of theocin acetate being 1 cg. The small doses of strophanthin, digitalin and digalen diminished diuresis. Glycosuria occurs in experimental

operations whether injections are made or not, especially if the test animal is narcotized. The glycosuria progressively increases during the tests. It is accompanied by polyuria increasing in proportion to the quantity of sugar excreted. The erroneous conclusion that small doses of the glucosids of digitalis produce diuresis in healthy animals is due to this glycosuric polyuria. The tracings are given.

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(1c—167)

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**The Action of Glucosids of the Digitalis Group upon the Isolated Heart of *Leptodactylus Ocellatus*.**

*O. M. Pico, Rev. Asoc. méd. argentina, Buenos Aires (Biol. Sect.), 35:78, May-June, 1922.*

The author carried out experiments to test the resistance of *Leptodactylus ocellatus* (the South American frog) to the action of crystallized strophanthin, ouabain, amorphous strophanthin, digitalein, spartein, hordenin, saponin, fluid extract of digitalis, and decoction of its leaves. The order in which toxic symptoms appeared was analagous to that seen in *Rana esculenta*: dissociation, increase of tonus, systolic arrest, with auricles dilated. When doses were highly concentrated, there was ventricular arrest in systole, without reaching the stage of dissociation. The isolated heart proved enormously resistant to the glucosids, sometimes 100 times more so than that of *R. esculenta*. To saponin it showed about the same resistance as *R. esculenta*, which suggests that saponins and the glucosids of digitalis act in an entirely different way from each other, in spite of the similarity of the symptoms to which they give rise. The differences of behavior in the individual hearts were so great as to prove that *Leptodactylus ocellatus* cannot satisfactorily be used for the titration of these glucosids.

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(1c—168)

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**Strophanthin. I. Strophanthidin.**

*Walter A. Jacobs and Michael Heidelberger, J. Biol. Chem., 54:253, Oct., 1922.*

The authors found that on reduction with palladium and hydrogen, strophanthidin yielded a dihydro compound,  $C_{23}H_{34}O_6$  which was isolated as a monohydrate and a dihydrate. Although the reaction required an unusual time for completion and a relatively large amount of colloidal palladium, it is believed probable that the point of attack was a double bond. The reduction of a carbonyl group seems excluded since only a monobenzoate was obtained by benzylation of the hydrogenated compound. Other workers have stated that strophanthidin reacts with ketone reagents but they were unable to isolate definite products. The authors prepared the crystalline oxim and the phenyl and p-bromophenylhydrazones of this substance which definitely prove the presence of a carbonyl group. From all indications this is ketonic in character. Finally, the authors' analyses show that isostrophanthidin, like strophanthidin, possesses when anhydrous the formula  $C_{23}H_{32}O_6$ . In accord with this, the formula of isostrophanthidin benzoate was found to be  $C_{30}H_{36}O_7$ . The authors conclude that strophanthidin, although it may have at least one double bond, possesses mainly a saturated alicyclic

skeleton. Of the 6 oxygen atoms, 2 are accounted for by the lactone group, 1 by a carbonyl group, and 1 by an alcoholic group.

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(1c—169)

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**The Cumulative Action of Crystallized Ouabain Arnaud.**

*C. Dimitracoff, Bull. d. sc. pharmacol., Paris, 29:489, Oct., 1922.*

The author has confirmed earlier conclusions concerning the cumulative effect of ouabain, by employing subcutaneous injections, the previous tests having been made with oral administration of the drug. Doses of 0.25 mg. and less were injected daily for some 8 days, 3 dogs being employed for the tests. There seems to be no doubt that ouabain has a truly cumulative action. The first effects of the drug to appear are anorexia, loss of weight, asthenia, often thirst and vomiting, and sometimes diarrhea. With daily doses ranging from 0.15 to 0.25 mg., death occurs when the total quantity injected subcutaneously approaches or equals twice the lethal intravenous dose. The average coefficient of daily elimination, per kilo body weight, is 0.0123 mg., or one-twelfth the lethal dose per kilo. If two-twelfths per kilo be given, death should occur on the twelfth day, if three-twelfths, death should occur on the sixth day, etc. Daily doses below one-twelfth the lethal dose should not produce intoxication.

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(1c—170)

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**Ergotamin, a Specifically Acting Alkaloid from Ergot.**

*E. Rothlin, Schweiz. med. Wchnschr., Basel, 52:978, Oct. 5, 1922.*

From animal experiments and chemical studies of ergotamin isolated from ergot it is to be assumed that the ergot action is due to the presence of chemical substances of an alkaloid nature. The lack of knowledge of other possible characteristics typical of ergot, and the lack of clearness as to its biologic characteristics, are due to the different qualitative and quantitative composition of the ergot preparations examined. On the assumption that ergotamin is a complete carrier of the ergot action and that it (or gynergen) is a constant solution free of nonspecific active substances, the author in his animal experiments made a study of the characteristics of the drug, which he reports: He first injected small physiologic doses of ergotamin intravenously (about 0.02-0.2 mg. per kilo) and then large toxic doses in different species of animals. He found that ergotamin in physiologic doses not only has a specific action on the uterus but that other organs with smooth musculature are also affected, though to a somewhat less extent. The author points out that an essential characteristic of ergotamin in large doses is an increase in blood pressure. The demonstration of blood-pressure changes with ergotamin is just as definite a physiologic evidence of the presence of specifically active principles in an ergot preparation as the action on the uterus which has long been known.

From his experiments, the author concludes that the specific action of ergot is not only the production of contractions of the uterus but an increase in blood pressure. In addition to its therapeutic effects, toxic actions can also be produced by ergotamin, but only by doses beyond the limits of those necessary for therapeutic purposes. The proteinogenous amins, tyramin and histamin, which in recent years have

generally been regarded as ergot substances with a specific action, have decidedly different physiologic and toxic characteristics and cannot be regarded as substances with a specific ergot action.

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**Is Asphyxia the Cause of Drug Hyperglycemias?**

*A. L. Tatum and A. J. Atkinson, J. Biol. Chem., 54:331, Oct., 1922.*

Before determining the rôle of asphyxia in the hyperglycemia produced by various drugs, the authors first studied the effect of simple asphyxia, without drug action. For this purpose carbon monoxid was used since it acts only by displacement of oxygen. As a measure of the asphyxia produced in cases uncomplicated by respiratory or circulatory disturbances other than asphyxial, the alkaline reserve was considered.

Cyanids are considered to produce another type of asphyxia by lessened oxidation in the presence of an abundance of oxygen. If cyanids depress intracellular oxidation, a study of the relation of their glycogenolytic activity to their production of acidosis should be important in connection with the relation of asphyxia and drug hyperglycemia. Accordingly, the authors injected sodium cyanid in the ear veins of rabbits and found a marked fall in the reserve capacity of blood with a relatively small rise in blood-sugar concentration. A summarized comparison of the actions of ether, epinephrin, carbon monoxid, and cyanids on the blood-sugar concentration and alkaline reserve capacity, demonstrates that cyanid and carbon monoxid (in other words asphyxia) produce a much greater fall in reserve and much less sugar rise than epinephrin or ether. Since the fall in reserve is presumably caused by diminished oxidation, the hyperglycemia of ether, epinephrin, carbon monoxid and cyanid cannot in each case be caused by diminished intracellular oxidation, if this is adequately measured by the alkaline reserve capacity. The fall in reserve should be a measure of the same diminution of oxidation which should lead to a relatively definite glycogenolysis, providing the circulatory and respiratory factors are not sufficiently altered as to vitiate the authors' interpretation. If this reasoning is logical it then follows that the hyperglycemia produced by ether cannot all be accounted for on the basis of asphyxia or acidosis. In regard to epinephrin there is absolutely no available evidence of any contributory action of asphyxia in hyperglycemia production by this drug. On giving epinephrin and ether simultaneously to rabbits, the authors found no demonstrable synergism but rather a summation of glycogenolytic effects indicating that the ether and epinephrin each produced their respective hyperglycemias by independent actions.

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(1c—172)

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**The Pharmacologic Action of Isopropylethylbarbituric Acid.**

*D. E. Jackson, J. Lab. & Clin. Med., 8:23, Oct., 1922.*

Within the limits of medicinal dosage the action of isopropylethylbarbituric acid is confined to the central nervous system, and especially to the cerebrum. This action can best be demonstrated by the

oral administration to dogs of increasing doses of the acid, which has been dissolved in water by the addition of a sufficient quantity of sodium carbonate. Under these circumstances the drug acts as an efficient and reliable somnifacient. Its action comes on in 20-40 minutes, and is manifested by an overpowering desire on the part of the animal to lie down quietly and to sleep. The dose required to produce a mild sedative effect in the average adult is 2 gr. If deep sleep is desired and the patient is in a highly excitable state,  $3\frac{1}{2}$  gr. may be given, or a large dose may be administered (4-5 gr.) and then small doses (2 gr. each) may be given once or twice daily thereafter. These small doses keep the patient calm and enable him to secure quiet, refreshing sleep. The drug (sodium salt) may also be administered hypodermatically in 2 gr. doses 2 or 3 times per day. Of the sodium salt (which is very soluble in water) the dose by mouth is 2-4 gr.

From the therapeutic action of the drug it seems obvious that man is more susceptible to its hypnotic effects than are dogs. In these animals the dose beyond which recovery does not occur is about 1 gr. per pound body weight. This indicates that the average patient might survive a dose of nearly 150 gr. The author suspects, however, that the fatal dose in man may be smaller than this, unless the stomach be emptied soon after the drug has been swallowed. The lower degrees of susceptibility possessed by dogs, as compared with man, probably holds only in the case of the higher, psychic areas of the cerebrum. So far as the heart, the other circulatory organs and the respiratory apparatus are concerned, it is probable that no great differences exist between man and the dog.

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**Barbital as an Anesthetic for Dogs.**

*Arthur L. Tatum and Eloise Parsons, J. Lab. & Clin. Med., 8:64, Oct., 1922.*

In routine class-room study of the hypnotic drugs, it was observed that with a sufficient dosage of barbital the effects, from depression to the state of complete surgical anesthesia, persisted beyond 24 hours. After 24 hours the animals were used for acute experiments. The blood pressure was entirely within normal limits, while the vasomotor responses were equally as good as those observed during ordinary light ether anesthesia. Pancreatic secretion was as good as that under ether while gastric secretion after secretin and renal secretion from diuretics were far superior to that observed under ether. Technic: Barbital sufficient to make 0.25 gm. per kilo body weight is dissolved in dilute sodium carbonate solution. This solution administered by stomach-tube produces surgical anesthesia in  $\frac{1}{2}$ -1 hour, which lasts for at least 8 hours. By avoiding an excess of sodium carbonate over that required for solution of the barbital, vomiting is not likely to occur.

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(1c—174)

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**Phenyltaurin and Its Higher Homologues.**

*R. Demars, Bull. d. sc. pharmacol., Paris, 29:492, Oct., 1922.*

For preparing phenyltaurin, a given weight of chlorethanesulphonic acid is placed in a small globular flask. Anilin is added, in small



quantities at a time. The reaction is energetic and liberates much heat. Anilin is continued, somewhat above the theoretical amount. The product becomes liquid and addition of water is unnecessary. The flask, closed with a perforated stopper receiving a long condensing tube, is heated on the oil bath at 130°-140° C. for 6 to 8 hours. The end of the reaction is determined by volumetric titration of the saline chlorin and the flask allowed to cool. The liquid is diluted with 10 or 12 times its volume of distilled water to precipitate the excess of anilin, decanted and placed in desiccators. It contains only phenyltaurin and anilin chlorhydrate. Large, dark brown crystals finally separate, but constitute a mixture. It is preferable to distil the uncrystallized mixture in a current of steam and an excess of barium hydrate, removing excess barium carbonate and hydrate when the reaction is complete. The liquid then contains barium chlorid and barium phenyltaurinate. Just enough sulphuric acid is added to precipitate barium sulphate and leave only HCl and phenyltaurin in the filtrate. The latter is evaporated to dryness, the last portions of HCl being removed by 3 rapid washings with 95% alcohol. The remaining phenyltaurin may be dissolved in water, then in alcohol, and crystallized finally. The important point is exact precipitation of the barium, avoiding excess of or too little sulphuric acid. Methylphenyltaurin and ethylphenyltaurin are prepared by the action of chlorethanesulphonic acid on methylanilin and ethylanilin. The process is similar to that just described, except that the heating temperature is from 130° to 135° C., and the product of the first reaction is immediately subjected to the steam distillation. The phenyltaurin crystals are light, silky, reddish-violet and reflect light brilliantly. Those of methylphenyltaurin are paler violet, anhydrous and melt at 239° or 240° C. Those of ethylphenyltaurin are greenish-white, very soluble in water, more soluble in hot than in cold alcohol, and anhydrous. The methyl and ethyl compounds dissolve copper hydrate only partially, certain oxidations occurring.

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(1c—175)

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#### **Studies on the Action of Barium.**

*William Salant and Nathaniel Kleitman, J. Pharmacol. & Exper. Ther., 20:247, Nov., 1922.*

Considerable evidence has accumulated to show that barium stimulates every form of muscle. Salant and Kleitman observed on several occasions that the action said to be characteristic of barium was absent, and a systematic study was made. Fresh frog hearts showed, when contracting vigorously and with normal frequency, no changes when perfused with solutions of barium chlorid; when their action was slow or irregular, they showed increased frequency and regular action when perfused. Fresh turtle hearts gave similar results. Mercurialization of frog hearts caused depression, diminished conductivity, and delirium cordis, and perfusion with solutions of barium chlorid increased this depression, but in turtle hearts so treated, the manifestations of mercury poisoning were in a measure antagonized. Aconitin caused powerful excitation of the heart, especially increasing the frequency. Perfusion with barium after use of aconitin caused a very pronounced diminution of amplitude and a considerable slowing of action in frog hearts, while

the behavior of turtle hearts was less constant. Perfusion with cocain caused slowing and partial heart-block, and perfusion with barium chlorid after cocain had no effect, though if the 2 were given together, some synergy was observed.

Segments of a cat's small intestine treated with aconitin showed contractions increased as to force and frequency. The effect of adding barium was a prompt contraction followed immediately by relaxation, and the rhythmic contractions seen before adding the barium were abolished, or became weaker and more frequent. Similar results were obtained using isolated rabbit intestine.

The conclusion drawn from this work is that the action of barium varies with the conditions of the organs and the state of the tissues with which it comes in contact. Others have shown that the action of barium on the heart was different according to its endocardiac or exocardiac application, and that these effects were due to the difference in permeability of the endocardium and exocardium. Observations on the permeability of the cell seem to indicate that both chemical substances and physical agents may cause changes in the permeability. Cushny advances the suggestion that similar factors resulting in changes in permeability to different ions might modify the action of barium to cause stimulation or depression.

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(1c—176)

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**Studies on the Pharmacology of Sodium Citrate. II. The Influence of Sodium Citrate on Peristalsis.**

*William Salant, N. Kleitman and L. H. Wright, Am. J. Physiol., 62: 531, Nov. 1, 1922.*

These observations include studies on the effect of sodium citrate on different parts of the intestine in situ, an inquiry into the mechanism of its action, tests on the uterus to ascertain the reaction of smooth muscle structures other than the intestine and experiments on segments of the isolated intestine suspended in Locke's solution. Cats, dogs and rabbits were the subjects, and urethan was the chief anesthetic. Chemically pure sodium citrate was injected in 3% solution intravenously, or 20% intramuscularly. The Trendelenburg method was employed for recording the contractions of the intestine in situ and also those of the uterus. The methods used in observations on the isolated intestine were essentially the same as those employed by Salant and Schwartz.

The authors found that the intravenous and intramuscular injection of sodium citrate stimulated the motor function of the intestines, but the action on the small intestine was greater than on the large intestine. The action of citrate also varied in different animals. Stimulation of tonus predominated in dogs' intestines; augmentation of the rhythmic contractions was largely observed in rabbits, while both occurred in cats. Experiments with citrate on the isolated intestine indicated that stimulation was the main effect in the rabbit's intestine and depression the most frequent result in the cat's intestine. Citrate was found to have no effect on the uterus in situ. Concerning the mechanism of the action of citrate, the authors found that after the administration of atropin the injection of citrates failed to produce any response of the intestine, which shows that the citrate must act on the peripheral nervous mechanism and not directly on the muscle substance.

(1c—177)

(1c—177)

**Morphologic Study of the Effects of Various Remedies on Trypanosomes.**

*P. Stefan, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:263, Sept. 25, 1922.*

The effect of a large number of remedies for trypanosomiasis, including representatives of various chemical series and normal human serum, was tested on some trypanosomes pathogenic to animals. An attempt was made to follow the effect of each remedy on the morphology of the trypanosome cells by studying Giemsa stained preparations. The remedies included compounds of arsenic and antimony: atoxyl, antimony tartrate, stibenyl; parachinoid; tryphenylmethane stains (parafuchsin, tryparosan); acridin stains (flavacid, trypaflavine); safranin stain (trypan red); "Bayer 205," and normal human serum. Primary protoplasmic lesions were effected by atoxyl, tryparosan, flavacid, trypaflavine and trypan red, as well as by trypasafrol, "Bayer 205," and human serum. A specific affinity of the nucleus was observed in the case of antimony tartrate and stibenyl. The effects of trypasafrol and trypan red were less certain. The blepharoplast was destroyed by parafuchsin, tryparosan, flavacid and trypaflavine. Mutual relations were observed between nucleus, blepharoplast and flagellum, the investigation of which will add to our knowledge of the processes taking place in the protozoan cell. Weak remedies stimulate the tendency to fission, as in the case of parafuchsin and trypasafrol. A number of incidental findings remain to be explained, as for example the blepharoplastic vacuole of the distended posterior ends, globular forms, and the gaping posterior extremities in normal trypanosomes. The examination of the split bodies of trypanosomes revealed the fact that the membrane of the trypanosome is torn into two parts by certain mechanical influences. The most rapid and intensive sensitiveness to remedies was exhibited by *Trypanosoma brucei*, the slowest by *Trypanosoma equiperdum*. Blepharoplastic vacuoles were observed principally in *T. equinum* and *equiperdum*, and less frequently in *T. brucei*. The same applies to the tendency to fission, which was also more pronounced in the two former species. Distended posterior ends were observed in all three species to the same degree.

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**A Study of the Colloidal Properties of Arsphenamin and Allied Products.**

*George W. Raiziss and Joseph L. Gavron, J. Pharmacol. & Exper. Ther., 20:163, Oct., 1922.*

In investigating the causes of the disturbing phenomena associated with arsphenamin therapy, the same procedure as that employed by Graham, in 1862, was followed, namely diffusion through animal or vegetable membranes. Arsphenamin dialyzed about 25 times more slowly than sodium chlorid. In methyl alcohol, however, the former diffused 4 times more rapidly than in water, probably due to the ability of the alcohol to break up the drug into smaller particles. Arsphenamin is apparently readily hydrolyzed in aqueous solution, since it was found that its chlorin ions diffused much more rapidly than the arsenical

compound. Thus, after 30 hours there was no chlorin within the parchment bag, while 81.14% of the arsenical still remained. The authors observed a similar hydrolysis with the corresponding sulphate. This is insoluble in water, but by suspending in water and subsequently filtering, all of the sulphuric acid was found in the filtrate. In this diffusion experiment, the arsenical remaining in solution within the parchment was 3,3'-diamino-4,4'-dihydroxy-arsenobenzene. In the dialysis of an alkalized solution of arsphenamin (disodium salt), the sodium ions diffused more rapidly than the arsenical. Although the more therapeutically important disodium salt of arsphenamin is more diffusible than the dihydrochlorid, it still possesses distinct colloidal properties, passing through the membrane 8 times as slowly as sodium chlorid and almost 4 times as slowly as disodium 3-amino-4-hydroxyphenyl-arsonate.

These 2 arsenicals differ in that the arsenic is in the pentavalent form in the arsonate and in the trivalent condition in the arseno-compound. Thus the trivalence of the arsenic seems to be an important factor with regard to both the therapeutic and colloidal properties of arsenicals. Neo-arsphenamin, which is so very soluble in water, possesses marked colloidal properties. In the first 12 hours but 10.27% of the arsenical diffused, as compared to 88.31% of sodium chlorid in the same time. Assuming that as an average 80% of the total sulphur in the drug is combined to the amino-groups and 20% uncombined, it was found after dialyzing for 36 hours that all of the free sulphur, 57.43% of the combined sulphur, and only 26.1% of the total arsenic passed through. As to the results obtained with silver and gold sodium arsphenamins, although 26.89% of the arsenic dialyzed, no silver was found in the dialysate. All of the metal remained within the parchment. Similar results were obtained with the corresponding gold compound prepared by the writers.

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#### **The Oligodynamia of Silver. IV.**

*R. Doerr and W. Berger, Biochem. Ztschr., Berlin, 131:351, Sept. 16, 1922.*

The bactericidal action of silver is increased by heating, by boiling several times in distilled water or by embedding the silver for several days in agar-gelatin. We are not dealing here with a distant action or a colloidal solution; the experiments indicate that there are formed, on the surface of the piece of metal, combinations whose water solubility causes their cytotoxic effect. It was found that the bactericidal strength of a prepared oligodynamic solution of activated water could be overcome by potassium cyanid; also that silver surfaces which had been treated so as to acquire a bactericidal action lost it when treated with potassium cyanid. This is due to the transformation into inactive  $\text{Ag}(\text{CN})_2$  ions of the silver ions that injure cells. Therefore the active principle in the different forms of oligodynamic experiment is the silver ion. This is in harmony with the dialyzability and diffusibility of the oligodynamic silver solution, as well as with Hoenigschmid's and Birkenbach's demonstration that water which has been in contact with silver surfaces has a chlorin reaction which can be demonstrated by nephelometry. There is no definite proof of the bactericidal action of

pure colloidal silver (without an admixture of Ag-ions). The bactericidal capacity of silver surfaces is brought about by the action of air on the metal. The active principles in the air are to be considered as CO<sub>2</sub> and O<sub>2</sub>, since both of these in a concentrated condition act much more rapidly and intensely on the metal than the air itself. A similar demonstration was made for copper by Wernicke and Sordelli.

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**The Influence of Chemotherapeutic Silver Preparations on the Physiologic Bactericidal Activity of the Human Total Blood in Vitro.**

*Hugo Kämmerer and Ludwig Schätz, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:298, Sept. 25, 1922.*

In dealing with substances whose effects on the living human organism are still so obscure as those of the silver compounds, any opportunity of gaining an insight into the nature of their action is welcome. According to Neufeld's observations, the bactericidal effects of chemotherapeutic remedies in vitro are paralleled by those in vivo. The authors conducted experiments to test this conclusion. The blood was withdrawn from the cubital vein and mixed with sodium oxalate (1:100), to prevent coagulation. The bacterial cultures employed for the experiment were bouillon cultures of 12 hours. The individual experiments were arranged according to the following scheme: full blood and bacteria alone; full blood, bacteria and silver preparation; bacteria (without blood and silver preparation) in ordinary bouillon; and silver preparation and bacteria without blood. Experiments were made with collargol, argochrom, argoflavine, fulmargin, dispargen, electrocollargol with and without the addition of various heavy metals. The bactericidal effects of the silver preparations in the quantities hitherto employed in adults, i.e. the leukocytal, catalytic and antitoxic effects which have partly been demonstrated and partly surmised, could not be demonstrated in the test-tube experiments with fresh total blood. The full blood neutralizes the bactericidal effect in vitro either completely or nearly so, probably in consequence of absorption by the corpuscular and colloidal elements of the blood, especially protein substances. The only exception is in the case of fulmargin, in its effect on paratyphoid bacilli. The addition of the silver preparations to the full blood does not appreciably diminish the vitality of the bacteria, which would lead to an increase of the physiologic bactericidal activity of the blood. Such activity, so far as it can be demonstrated at all against the various bacteria, is not affected in any way by the silver preparations in the dilutions ordinarily employed for therapeutic purposes.

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**Observations on Experimental Intestinal Tuberculosis. The Effect of Treatment with Naphthalene Emulsion.**

*T. Redman, J. Path. & Bacteriol., Edinburgh, 25:433, Oct., 1922.*

The object of the author's experiments was to test the therapeutic value of naphthalene emulsion in intestinal tuberculosis, to ascertain



whether it had any retarding effect upon the rate of progress of the disease. The emulsion used had the following composition:  $\mathcal{R}$  Ol. Naphthal.  $\mathfrak{z}$  i, Liq. Potassae  $\mathfrak{z}$  i m xl, Aq. ad  $\mathfrak{z}$  iii. Ol. Naphthal. was prepared by dissolving naphthalene in warm olive oil and allowing excess to crystallize out. In vitro it was found that 20 c.c. naphthalene emulsion killed half a slant of a virulent culture of human tubercle bacilli in less than 12 hours, as shown by failure to produce the disease in a guinea-pig upon inoculation. In testing the therapeutic value of the naphthalene emulsion on living animals suffering from tuberculosis the general procedure was to administer daily a constant dose (one dram) of naphthalene emulsion for 7-10 days after varying periods subsequent to infection. By feeding guinea-pigs with fresh, heavily infected sputum in a bran mash a slowly progressing, ascending infection of the alimentary tract was achieved. The animals were killed at different dates to observe the effects of the naphthalene emulsion, a postmortm examination being made on each animal. The author observed that no trace of tuberculous infection of 20 days' standing could be found 14-70 days after the use of naphthalene emulsion. Infection of the spleen was prevented for 54-75 days, while the liver and lungs were protected from infection for about 115 days after ingestion by the animal of the tuberculous material. Microscopically, there was a marked difference between the later stages of the tuberculous glands of treated and untreated animals, the formation of fibrous tissue occurring fairly early and replacing the typical tubercle structure in the treated animals much sooner than in the untreated animals in many cases. In the very early stages the naphthalene treatment may eradicate the disease.

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**The Comparative Concentrations of Alcohol in Human Blood and Urine at Intervals after Ingestion.**

*Walter R. Miles, J. Pharmacol. & Exper. Ther., 20:265, Nov., 1922.*

Widmark has asserted that the concentration of alcohol in urine excreted in short intervals after ingestion agrees very well or completely with that in the blood, and that a knowledge of the alcohol content of the organism could be obtained from the urine while Grehant and Schwiesheimer contend that the curve for alcohol concentration in the blood is parallel with that for the intensity of alcohol effect. The author has studied the problem of the comparison of blood and urine. The Widmark-Nicloux method of alcohol determination was used, and experiments were made on groups of abstinent people, moderate drinkers, and habitual drinkers.

Work done on abstinents and moderate drinkers showed that, following ingestion of 27.5 gm. alcohol in 1000 c.c. of diluent, the concentration of alcohol in the urine was higher by 50% than that in the blood, and higher by 25% than that in the plasma, for 40 minutes to 2 hours. The same amount of alcohol taken in more concentrated form gave higher concentrations in blood, plasma, and urine. The alcohol concentration in blood and urine reaches its maximum 60-75 minutes after ingestion. The concentration in the plasma is 20-25% higher

than that in whole blood, and when the kidney secretion is slight, the concentration in the urine may be reduced to about the same level as that in the blood. A study of habitual drinkers showed that the alcohol concentration in blood and urine, after taking 27.5 gm. diluted or concentrated, is not identical, and does not run parallel in the 2 hours following ingestion. At first the alcohol concentration in urine is about that of the blood but in 40-60 minutes it rises and remains so for an hour. In the typical habitual drinker, the concentration in urine, blood, and plasma is higher at every point with the more concentrated dose. Subjects thoroughly habituated absorb dilute doses about the same as nonhabituated persons.

The percentage of alcohol eliminated in the urine in the first 2 hours after ingestion is 1.2-1.6 of that taken, and the major portion of elimination occurs in this period if the bladder is emptied 2 or 3 times. Both blood and urine reach their maximum alcohol concentration at the same time, and while not identical, the urine-alcohol curve is useful for the comparison with the time relations of objective measurements of the alcohol effect on the central nervous system.

## TOXICOLOGY

(1c—183)

(1c—183)

### **The Comparative Toxicity of Ammonium Salts.**

*Frank P. Underhill and Robert Kapsinow, J. Biol. Chem., 54: 451, Oct., 1922.*

The comparative toxicity of the more common ammonium salts, both organic and inorganic, was studied on adult white rats of average weights. All the salts used were made to approximate 5% solution. The amount of nitrogen in the form of  $\text{NH}_3$  in 1 c.c. of 3 of the solutions was accurately determined. Six animals were used for each series, the amount of solution injected ranging from 0.5 to 3.0 c.c. per 100 gm. body weight. The minimum lethal dose was viewed as that amount which caused death within 3 hours. The tabulated results show that the toxicity of ammonium salts is directly proportional to the amount of  $\text{NH}_3$  present. The greater the ratio of  $\text{NH}_3$  to the salt, the smaller is the minimum lethal dose, while the fatal acting time is inversely proportional to the amount of  $\text{NH}_3$  present.

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### **The Toxicity of Aromatic Nitro Combinations (Dinitrobenzol).**

*Joseph Stukowski, Deutsch. med. Wchnschr., Leipsic, 48: 1377, Oct. 13, 1922.*

The author discusses the symptoms of dinitrobenzol intoxications in connection with a series of cases in a factory which utilized explosives (the patients were brought in with dyspnea, cyanosis, brown discoloration of the skin, vomiting and stupor). According to Hübner, 2 symptom complexes control the picture of this intoxication: (1) the

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nervous phenomena; and (2) the cardiac affection in association with circulatory disturbances. The subjective symptoms are dyspnea, palpitation, pains in the joints and head, lassitude, lack of energy, increased irritability and nausea.

The visual and auditory disturbances described by other authors were not present in any of the 9 cases of the aforesaid series. Convulsions were observed in only 1 case: they occurred on admission and were never observed again. In their nature they resembled epileptic attacks. In all the 9 cases, the examination of the heart revealed a systolic murmur at the apex which was not audible over the other openings. The second pulmonary sound was not markedly accentuated. A widening of the heart toward the right or left was not demonstrable. The pulse was moderately high, moderately full and regular (60-80). In the blood the author found an enormous increase of resistance of the erythrocytes, leukocytosis, anisocytosis, slight poikilocytosis and polychromatophilia. The blood was chocolate brown in color and the serum was discolored dark with a shade of brown. The color index was less than 1.00 in 5 cases and in 1 case it was 1.06. The hemoglobin content was 52-66%. The blood pressure was not materially changed. The urine was discolored dark and contained neither albumin nor sugar and no blood; urobilin was present in 3 cases, but bilirubin and urobilinogen were always negative. The sediment was normal. On the first day of observation there were slight rises of temperature (37.2 to 37.9° C.) in all the cases, but these fell below 37° C. on the next day. The patients recovered so rapidly that they were discharged at their own request on the second day, at the latest on the eighth day. One patient was affected after 10 days by a second intoxication from which he recovered just as rapidly as from the first, without sustaining any permanent injury. Subsequent examinations of the patients showed no traces of permanent injuries.

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#### **The Edema of Paraphenylendiamin.**

*O. S. Gibbs, J. Pharmacol & Exper. Ther., 20:221, Oct., 1922.*

Attention was originally directed to paraphenylendiamin in consequence of its poisonous effects when used to dye hair or furs. Preliminary experiments in rabbits produced edema of the head and neck sufficient to cause death from asphyxia. The dose used in the author's experiments was 0.1 gm. per kilo body weight when given by stomach tube; for intravenous use a dose was calculated to give approximately 1:1000 in the blood stream. Edema appeared 1-1¼ hours after administration of such dose, first noticed under the tongue and extending rapidly to the neck, accompanied by increasing respiratory difficulty and swelling of the glottis and vocal chords. This is the initial stage of a general edema. The nervous system influences the edema production only indirectly by changing the blood supply. Atropin in doses sufficient to paralyze the parasympathetic nerves does not antagonize the action of paraphenylendiamin. That the latter has an effect on the blood is shown by the shortening of the clotting time. The edema of paraphenylendiamin is closely imitated by that induced

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by the perfusion of an animal with Ringer's solution, showing that the action of the drug is a general one, either on the blood-vessels or on the blood.

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**The So-Called Habituation to "Arsenic": Variation in the Toxicity of Arsenious Oxid.**

*Erich W. Schwartz, J. Pharmacol. & Exper. Ther., 20: 181, Oct., 1922.*

Experiments upon rats, rabbits and chickens have shown that the toxicity of different preparations of arsenious oxid administered undissolved per os varies markedly owing to the coarseness or fineness of their subdivision. The finer the particles of a preparation, the more potent it is, and vice versa. For the mammals used (rats and rabbits), the preparations consisting of the larger particles, when given in suitable amounts, produce death more slowly than those consisting of smaller ones. Preparations consisting of large particles are relatively more toxic for chickens than for these mammals. Experiments upon cats have shown that potency of arsenious oxid (administered undissolved) to cause emesis also depends upon the state of subdivision of the preparation used. No generally valid statement as to the size of the exact lethal dose of undissolved arsenious oxid administered orally can yet be given. The toxicity of each preparation must be determined experimentally, although it may be possible to estimate it approximately by determining the fineness of the arsenic with a low power microscope. It is unsafe to judge this point by the naked eye because a preparation which appears fine may consist of particles so large as to possess relatively slight potency. The mere consumption with impunity of large doses of undissolved arsenious oxid is not proof that habituation exists. The toleration of such large doses may be due not to any attribute inherent in the consumer (immunity), but to an attribute inherent in the preparation consumed, namely, its relatively slow solubility, which has been further decreased due to its coarse state of subdivision. In order to establish in a given case without chemical data the fact that habituation (fictitious or real) has developed, it is therefore necessary to proceed in the following way: Determine the oral lethal dose and report the precautions taken in determining the same; then demonstrate that the animal supposed to have been habituated is able to tolerate either more than this dose or more than the lethal dose of dissolved arsenious oxid. If this can be demonstrated, the conclusion that habituation (fictitious or real) has developed would be justified. In none of the reports of experiments with undissolved arsenious oxid which state that habituation occurs, have the requirements just outlined been fulfilled. Results can all be explained as reasonably by assuming that preparations of arsenious oxid of variable and relatively low toxicity were employed as by assuming that habituation had occurred. This is the more probable as no investigator has yet been able to demonstrate conclusively the development of any certain degree of habituation to dissolved arsenious oxid. It is the contention of the writer, however, only that habituation of higher animals

has not been proved, and not that it cannot exist. The doctrine of habituation, however, is open to serious question.

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**Chronic Arsenic Poisoning.**

*U. G. Bijlsma, Nederl. Tijdschr. v. Geneesk., Haarlem, 66: 1729, Oct. 14, 1922.*

In the cases of arsenic poisoning discussed by Elzas in 1921 and 1922, the point of view was that of diagnosis. The author views these cases from the standpoint of hygiene and public health. The Arsenic Commission did not find chronic poisoning from arsenic present in fabrics, wallpaper, etc., common in Holland. The Commission's report of a case of polyneuritis, as in a similar case reported by Ebstein and cited by Elzas, may, after all, have been fully warranted. Fatal results from quantities of arsenic so small as those mentioned in the cases of Elzas and Ebstein are not reported in the general literature. Moreover, in Ebstein's case nephritis proved to be present at autopsy. The literature does not show the production of nephritis by very small quantities of arsenic. It is regrettable that there was no autopsy in Elzas' case.

Elzas' case was seemingly not one of arsenic poisoning. Elzas probably bases his conclusion on the presence of arsenic in the urine, and may have been influenced by the Swedish report, made in 1912, and attributing arsenic poisoning occurring in Sweden to arsenic contained in zinc compounds exported from Holland. The Swedish report was devised as protectionist propaganda against Holland zinc. Following the report of the Swedish commission, a large number of cases of arsenic poisoning flooded the literature. Even Dutch physicians were not immune to this suggestion. In Raw's series, the method of determining arsenic was not described. Possibly it was present in cases where considered absent. Again, the Swedish report attributed certain cases to arsenic poisoning, notwithstanding the fact that the quantity of arsenic found in the urine was much less than the amount given as normal by Bang. It seems clear that the true condition present in these cases was a phobia entertained by the attending physician. The low quantity sometimes reported may be due to differences in locality or error in technic. Arsenic is excreted through many channels (urine, sweat, cutaneous epithelium, hair, nails, etc.), but mainly in the urine, feces and sweat. The route of excretion depends on the route of entrance. If any one route of excretion is closed, the others will be more active. Remembering chemical facts and determinations, a person excreting no arsenic in the urine is not in danger in the presence of a fabric containing 3 mg. arsenic per square meter. Elzas' second paper fails to convince that his case was really one of arsenic poisoning.

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**Lead-Poisoning from Face Enamel.**

*Henry W. Woltman, J. A. M. A., 79: 1685, Nov. 11, 1922.*

The author reports the case of a 38 year old female, married 20 years but never pregnant, who presented herself at the clinic

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complaining of paralysis of the hands. She gave a history of tremor of the upper extremities of 5 years' duration, gradually increasing in severity, a history of nausea and vomiting of 4 years' duration, eventually occurring almost daily. She had pains in both arms, thighs and legs and could not sleep. On examination the patient showed extreme emaciation, marked weakness of the upper extremities, a bilateral wrist drop, sclerotic arteries and dark stippled pigmentation over the gums. A diagnosis of lead poisoning was made. The patient admitted having used for 12 years a toilet cream which on analysis showed a very high lead content.

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**A Case of Tetany Accompanying Poisoning by the Field Narcissus.**

*E. Martin-Sans and de Verbizier, Bull. d. sc. pharmacol., Paris, 29:497, Oct., 1922.*

The field narcissus, cooked for a meal by mistake, was eaten by an entire family, of whom all but a boy of 14 received prompt treatment. The latter suffered from diarrhea and abdominal pain. During the several following days, 2 typical crises of tetany occurred, with rise of temperature to 38.5°. Chvostek's and Trousseau's signs could not be elicited. Appropriate intestinal treatment produced satisfactory cure. The patient had previously suffered from enteritis, a predisposition therefore existing. The plant producing the poisoning was *Narcissus pseudonarcissus* L. A long time ago Orfilia stated that this plant was emetic, affected the nervous system and might produce grave symptoms. The authors' case confirms these findings. Narcissus is not a perfectly safe drug. The Arab practice of applying the crushed bulb to burns is not without danger.

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**Report of a Case of Phosphorus Poisoning from Sucking a Spit-Devil.**

*A. S. Corwin, New York State J. Med., 22:475, Oct., 1922.*

A child of 3 years had a spit-devil in her hands which she evidently had had in her mouth. The mother immediately rinsed her mouth and hands, and freed her of all traces of the toy. After a lunch of carrots and potatoes she played about normally for about 4 hours, then walked a mile or so. On her return home she vomited, at first the lunch, and then a clear fluid. She continued to vomit frequently until early morning. No physician was called as the attack was thought to be an ordinary stomach upset. Castor oil and castoria were retained. The child was thirsty but ate nothing all day. She felt well enough to play and talk and to get out of bed at times. At 5 p. m. she had a convulsion which lasted 15 minutes, followed by coma, from which she never came out. A physician was called and produced emesis. The vomitus was brownish fluid but there was no food. In the evening the coma was less marked. Vomiting recurred occasionally through the night. Before 1 o'clock the next morning the bowels moved normally. At 2 o'clock

an enema with ox-gall brought away some brown fluid like that which had been vomited. The fluid was not typical coffee-ground material, but was undoubtedly altered blood. The temperature, pulse and respiration up to this time had not increased. Between 12 o'clock that night and 5 o'clock the next morning 5 more convulsions set in. At 5 o'clock a large quantity of brown fluid was vomited. At 6:30 the child was cyanotic, especially over the abdomen; temperature was 103° F. and pulse 130. The stomach was washed out and stimulants administered. Coma was profound and death occurred from respiratory paralysis at 9:15 a. m., about 46 hours after getting the spit-devil in her hands. Autopsy showed a huge yellow liver (greasy on section) and fatty degeneration of the kidneys, heart and intestinal wall. Peyer's patches were enlarged. A test of the spit-devil disclosed phosphorus, which reminded the father that the first vomitus had smelled of phosphorus. The spit-devil consists of a cartridge of folded paper in which is a mixture of magnesium carbonate, potassium chlorate, glue and phosphorus (10%).

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#### **Argyria and Collargol.**

*H. Koller-Aeby, Schweiz. med. Wchnschr., Basel, 52:983, Oct. 5, 1922.*

The author criticizes Tobler, whose report on chronic universal argyria and cases of death after intravenous and peroral collargol treatment might arouse alarm. It should be pointed out that Tobler found only one other case in the literature; in Crispin's case the silver was given by mouth and in his own case an extraordinarily large amount of silver was given by mouth. Injuries are not to be ascribed to the silver itself but to its improper use. The peroral administration of collargol is based on the mistaken assumption that it acts in the body as colloidal silver. It seems to have been shown that it does not pass from the stomach or intestine into the body in a colloidal condition and act there as colloidal silver. But also the widespread opinion that silver given intravenously acts as colloidal silver may be mistaken. The importance of the colloidal condition lies probably in the fact that metallic silver can only in this way be introduced expediently into the body. It is known from different experiments that silver disappears from the blood not because it is precipitated in the blood itself but because it can be absorbed from the blood by different organs and histologic elements. In this way it is deposited and stored in the body, which means that it is no longer colloidal silver but simply very finely divided metallic silver.

The skin argyria which has been known for a long time and which Tobler puts on a par with storing of silver as an acute argyria can, like the latter, be said to be perfectly harmless, as it never shows toxic actions. The injury is purely of a cosmetic nature. As an explanation of the fact that the typical argyria of the skin evidently occurs only from internal use in some form, the author assumes that the silver ion in the skin is deposited by a photochemical route (light catalysis) and remains deposited. Tobler's work, therefore, does not prove the danger of silver but rather its extraordinary harmlessness in comparison with other preparations in the pharmacopeia.

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**Presumptive Test for the Etiologic Factor in Bacterial Food Poisoning.**

*Victor Burke and Charles W. May, J. A. M. A., 79: 1669, Nov. 11, 1922.*

The causes of food poisoning may be roughly classified into 4 groups as regards diagnosis: (1) bacterial toxins; (2) organisms of the paratyphoid-enteritidis group; (3) ptomains and naturally poisonous foods (as toadstools), and (4) chemical poisons, mainly the poisonous metals. The authors attempted to develop a rapid test for the etiologic factor in bacterial food poisoning, of such a practical nature that it could be readily applied by a physician without the aid of a diagnostic laboratory. Experiments indicate that bacteria of the paratyphoid-enteritidis group are frequently infectious for rabbits when injected intravenously. Ordinarily it is not necessary to filter food juice before injection intravenously into rabbits for these animals are not affected by finely divided particles that will pass through the needle. If organisms of the paratyphoid-enteritidis group are present, death of the rabbits may occur in 10-12 hours, or may be delayed several days. Mild symptoms may appear in a few hours, owing to endotoxins present, followed by a return to a normal condition with a later development of symptoms as an infection develops. If, following the injection, some of the rabbits show symptoms and others do not, the naturally poisonous foods and poisonous metals not affected by heat, acid or alkali are excluded from consideration, and botulinus toxin and infectious organisms must be considered. A confirmed test for the presence and type of botulinus toxin can be made only when the antitoxin is available.

The authors remark that the tests should be made with the suspected food, if any is available. If not, the food container may be washed with a small amount of salt solution and this injected. In testing dry foods, extracts should be made with salt solution. If neither the food nor its container is available, the vomitus or stomach contents or the blood may be used.

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**Cumulative Action of Cobra Venom.**

*Arthur R. Cushny, J. Pharmacol. & Exper. Ther., 20: 233, Nov., 1922.*

In work on cobra venom, Yagi and Cushny found great difficulty in immunizing rabbits. In a number of experiments Cushny finds that the venom presents a cumulative action similar to that of digitalis and its allies, and of such inorganic poisons as mercury, arsenic, and lead. The venom was injected intravenously. It was seen that a concentration in the tissues of 1 in 5 million was harmless, while 1 in 4 million was fatal. Small doses, even as much as one-fifth the minimum lethal dose prove fatal if given repeatedly. A single minute dose was sufficient to cause very serious or fatal symptoms in animals which had been treated with the same dose for some time previously. The "discharge" of the poison from the body is fairly rapid at first, becomes

slower later, and the last traces are eliminated with difficulty, so that it would seem that part of the venom was free in the tissues first and could be readily excreted, while part is in some form of combination, and is retained. As to whether anaphylaxis was the cause or a contributing factor in the deaths seen after the use of the venom, Cushny says that the minute size of the initial dose and the fact that the symptoms did not follow immediately on the second injection, show that the symptoms were due to cobra venom, and not to anaphylaxis. Venom given in small quantities, frequently repeated, is retained to a lesser degree than when larger quantities are given at longer intervals. There were no evidences of either tolerance or immunity in Cushny's experiments.

One of the most marked symptoms in venom poisoning is the apparent exhaustion of the animals, due to partial paralysis of the nerve-endings, and death occurs from paralysis of the terminations of the motor nerves as in curare poisoning. During the cumulation of the venom, it is stored in the motor nerve-endings but does not impair their conduction enough to cause symptoms. When curarine action is superposed on that of cobra venom, the animal dies of a comparatively small dose. The venom may not be actually anchored in the nerve-endings, but its effects may be due to its concentration in the fluids surrounding them. Transfusion experiments by Cushny strengthen the belief, however, that the venom is anchored in the nerve-endings or receptors in striated muscle.

## 1d. BACTERIOLOGY AND PARASITOLOGY

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### A "Supermicroscope".

*Charles S. Thomson, Med. Officer, London, 28: 161, Oct. 7, 1922.*

This "supermicroscope" has been developed by Davidson of the Queckett Microscopic Society. It largely solves the problem of high eyepiece magnification without losing resolution, and permits the use of a higher power on any objective than the so-called N.A. law supposedly permits. This high eyepiece magnification is obtained by utilizing the existing compound microscope as an eyepiece, thus using 2 microscopes tandem fashion. The supermicroscope overcomes interference with the perfection of the original image by placing an achromatic system, called a "collector," between the 2 objectives. In this way the aerial image of a microscopic object is projected to a certain distance beyond it, dependent upon the distance of the "collector" from the front or "primary" objective. In a demonstration with slides of tubercle bacilli, gonococci and cholera bacillus showing flagella at a magnification of 1300 with a  $\frac{1}{8}$  in. objective having an N.A. of 0.82, the result surpassed images made with a  $\frac{1}{12}$  in. objective. This modification avoids the "messiness" of oil, gives an extra working distance of  $\frac{1}{8}$  in. against that of  $\frac{1}{12}$  in. O.G., and affords a much flatter "field" than with a  $\frac{1}{12}$  in. at the same magnification. It overcomes the vital question of "tube length." An uncovered object can be critically examined, which is not possible with modern microscopes. In low or medium power work the supermicroscope provides views with remarkable "depth of focus," and for certain biologic observations the

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combination of this feature with large "field" and long working distance is valuable. The supermicroscope is adaptable to photomicrography. The eyepiece of the microscope is never used and any desired magnification can be obtained direct from the optical system; therefore, no long extension camera is necessary and exposures are reduced.

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**Are the Active Principles of Filter-Passing and "Ultramicroscopic" Viruses Living Organisms or Enzymes?**

*H. M. Woodcock, J. Roy. Army M. Corps, London, 39:245, Oct., 1922.*

The author contends that certain granules, which Gordon has described and thinks are filter-passing microorganisms, are in reality granules representing the breaking down (by lysis or digestion) of organized material. The chief characteristic of these minute granular bodies seems to be that they stain best and most readily with Giemsa, and it is extremely important that due emphasis should be laid on the care and caution necessary in interpreting results obtained by this method of staining. It is highly probable that all living organisms contain chromatin, but everything that stains red with Giemsa is not chromatin and unless an element retains a stain recognized by cytologists as a nuclear stain, it must be gravely doubted whether such a body contains chromatin. An important question, therefore, is whether all these various granular bodies, which stain red with Giemsa, contain chromatin or not. Woodcock presents microphotographs from which he deduces that breaking down epithelial cells show a progressive disintegration of the nucleus, and the cytoplasm of such cells contains numerous little masses and granules of red-staining material, in all transitional stages. The color is of the same quality throughout.

Experiments with iron-hematoxylin staining lead to the inevitable conclusion that these minute bodies do not contain chromatin—not, at any rate, as we know it to occur, and on this ground alone they cannot be considered living organisms. These bodies are entirely comparable in nature and origin with the various bodies, of all types and sizes, which Woodcock has previously described as platelet-granules, Rickettsia bodies, and the inclusions in Kurloff's bodies, Negri bodies, Guarnieri's bodies, etc. All these stain red with Giemsa and remain unstained after a precise nuclear stain. These lymph granules may be derived from 2 sources: in part from the ultimate destruction of the epithelial cells, and in part from the inclusions in the vaccinia-bodies, representing the ultimate particles into which the ingested and altered corpuscles and cells eventually disintegrate. Such granules would probably be found, for instance, in the virus of hydrophobia.

The author reiterates his former view that the cause of virus diseases may be a ferment or enzyme, in support of which he cites the phenomenon of the "bacteriophage" of d'Herelle. In spite of all the experimental evidence regarded by d'Herelle as conclusive of the occurrence of a parasitic, ultramicroscopic organism producing this phenomenon, the general view is in favor of a bacteriolytic enzyme as the cause. Particularly with reference to the mode of increase of the ferment-virus in these diseases is the example of the bacteriolysin of



Twort-d'Herelle so valuable. To infer a similar mode of increase by the tissue cells involved in different cases, is not unreasonable. Excluding the idea of a parasitic bacteriophage, the only other way in which the bacteriolysin can be increased so abundantly as to destroy culture after culture is by the further production of the lytic enzyme by the bacteria affected. Although these bodies are not definite organisms, they stand in a fundamental pathologic relation to diseases considered by Woodcock as due to "hematophagy" and "hemtoboly"; they indicate the virus, that is they are the only objective manifestation thereof. These viruses can be cultivated only in tissue-containing mediums; a process takes place entirely comparable with what is seen in cultures in which the bacteriolysin is acting, that is a culture containing both ferment virus and cells (tissue cells, blood-cells or vegetable cells). As a result, more protein granules, end-products of the digestion, will be met with in the culture.

This general thesis is capable of extension, so that it may be usefully applicable to influenza. If the action described takes place in influenza, some of the difficulties in the way of regarding a known incriminating microörganism as the causative agent may be explained. On this view, of progressive autocytolytic action by a ferment originating from an unrecognized microbe, "cultivation" and further production of the ferment, granular end-products of the digestion and so on could take place in mediums containing a suitable cellular element, which had been inoculated with filtrates of secretions from which the actual causative organism had been eliminated. Moreover, since this autocytolytic action had been set in motion, it might be transmissible through series of animals, and certain animals might be more susceptible to this virus than to inoculation with the specific organism.

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#### Discussion on Mutation of Species.

*William B. Brierley, Brit. M. J., London, p. 722, Oct. 21, 1922.*

Every change in an organism is not mutation. In the strict sense it is a change in the fundamental nature of one or more hereditary units; in the wider sense it is a change in genotype due to abnormal distribution of hereditary units. A change originating in normal distribution of hereditary units in crossing, or as a result of redistribution due to the appearance of any form of genetic impurity in the parent individual, is not a mutation. The proof required to establish biologic mutation is no less precise than that required to establish chemical mutation; and like the latter is dependent upon analysis of the original and the derived products. The concept of mutation held at present by most microbiologists cannot be equated with that held by genetic students of higher forms. It is a more nebulous and inclusive concept, for their subjects have not yet been found susceptible to factorial analysis by cross-breeding, and detailed cytologic information regarding the genetic structure and behavior of the hereditary mechanisms is not available. In the protozoa and fungi there is the possibility of the origin of apparently new and distinct strains in the normal cytologic processes, and it is suggested that apparent mutations may be due to the selective isolation of such strains. In the bacteria it is suggested

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that a similar hypothesis is the most feasible on which to interpret present data; and that it will explain the facts of variation and mutation, bringing them into line with genetic concepts. The possibility of mutation in microorganisms cannot be denied, but no adequate proof of such mutation has yet been adduced, nor can be in the present state of our technic and knowledge.

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**The Intimate Structure of the Bacterial Cell.**

*David Ellis, Brit. M. J., London, p. 731, Oct. 21, 1922.*

Information cannot be derived from a single species; the final picture is built up from material supplied from several sources. The lower bacteria consist of 3 distinct groups: (1) Bacteriaceae, including the rod forms; (2) Coccaceae, including the spherical forms; (3) Spirillaceae, including the spiral forms. In the bacillus, most typical of Bacteriaceae, the cell is delimited on the outside by a sharply defined membrane; the body of the cell is made up of cytoplasm, which is not homogeneous. Staining shows a vacuolar network, in which doubtless are located substances found in the vacuoles of higher plants—raw materials, reserve materials, and other metabolic products. The 3 main reserve materials found are volutin, glycogen, and oil globules. The question of the presence of a specific nuclear body is still a vexed one. As is well known, bacteria reproduce asexually by formation of spores inside the cell. In support of the contention that the bacterial cell possesses a nucleus, the fact may be deduced that the small round object found in the middle of the spore area becomes a body endowed with life. Outside the sharply defined membrane is a covering, normally very thin, of mucilaginous matter. The structure of the coccus tallies closely with that of the bacillus; methods of cell division and spore formation are identical. The spirillum differs from these groups: Cell division takes place by separation of the cell into 2 completely rounded off portions connected by a thick bridge of mucilaginous matter, which finally breaks; formation is rapid. The thread bacteria are distinguished from the lower bacteria, in some forms by the cohesion of the cells to form a community, in others by the greater length and size of the cells. The cause of cohesion is traced to the development of the mucilaginous covering, which hardens and prevents the escape of dividing cells.

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**Differences between Mitochondria and Bacteria.**

*Edmund V. Cowdry and Peter K. Olitsky, J. Exper. Med., 36: 521, Nov. 1, 1922.*

The suggestion that mitochondria are in reality symbiotic organisms, would, if verified, exercise a profound influence in biology and medicine. The authors have accordingly attempted to make a direct comparison of the Janus-green reactions of mitochondria in living lymphocytes and of bacteria under identical conditions. *Bacillus proteus*, *Streptococcus hemolyticus*, *pneumococcus*, *Bacillus megatherium*, *Bacterium pneumosintes*, and *Bacillus tuberculosis* (human) were selected

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as widely representative. In each case a very small amount of blood from the ear of a rabbit was placed on a slide; to this was added, with a pipet, a small drop of bacterial emulsion and a solution of Janus green B of known concentration in 0.85% saline solution. By this method the reactions of living organisms and of mitochondria within living cells may easily be compared side by side and under identical conditions. It was soon found that the mitochondria in living lymphocytes surpass all the organisms examined in their affinity for Janus green. The study of living lymphocytes with their mitochondria intensely stained, surrounded by organisms which have not taken up any of the dye, leaves little room for doubt that in this respect the reactions of mitochondria and bacteria are entirely different.

For a direct comparison in fixed and stained preparations, the pancreas of the rabbit was selected as a tissue in which the mitochondria are well known. The above named organisms, suspended in saline solution, were injected with a hypodermic syringe into the substance of small pieces of this organ, just after its removal from the body. Immediately thereafter the fragments were fixed and stained in a variety of ways. Ordinary fixatives in every-day use in cytology and in bacteriology were employed. Regaud's fluid, Bensley's acetic-osmic-bichromate mixture, and Altmann's fluid proved to be the best preservatives for mitochondria. The bacteria, on the other hand, resisted the action of all the 10 fluids used. In these preparations the distinction between solubility of mitochondria and that of bacteria was often very sharp. There is also a pronounced difference in staining reaction. Giemsa's stain, which is perhaps the best adapted for bacteria, colors mitochondria little, if at all; this points to a fundamental difference between mitochondria and bacteria, and, in addition, there are other differences. In mitochondria definite spores and capsules have not been noted. Motility due to flagellate action has not been observed. The temperature, oxygen, and food requirements of mitochondria can only be expressed in terms of the requirements necessary for the cell as a whole. No mitochondria are known to resist a temperature of over 50° C.; neither is there any parallelism between mitochondria and bacteria in their relation to fermentation and to disease. In fact, the tendency of mitochondria is to decrease rather than to increase in diseases of infectious nature. Furthermore, there is no reason to believe that they possess the power of independent and characteristic growth apart from cells. The suggestion that mitochondria are independent microorganisms rests upon no other evidence than a slight similarity in form of substances of about the same size.

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#### **Hypersensitiveness Experiments on Bacteria.**

*Alfred Schnabel, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96: 351, Sept. 25, 1922.*

The author bases his experiments on the consideration that, if it be possible at all to hypersensitize bacteria against effective substances, the possibility of the habituation of the bacteria within a few hours to poisons, and the probable connection between habituation and hypersensitiveness, should make it possible to achieve this with ordinary 1 day cultures. The results of the experiments were demonstrated by the

methylen-blue staining method with pneumococci, staphylococci, dysentery bacilli, and colon bacilli. The effective substances employed were optochin, sublimate, formaldehyd, quinin, phenol and silver nitrate. Pneumococci cultivated in tubes of serum bouillon of different optochin content exhibited after an incubation of 24 hours at 37° C. 2 or 3 zones of sensitiveness deviating from the norm. Cultures raised in higher optochin concentrations (1:500,000 on the average) became resistant against optochin, whereas those raised in comparatively lower concentrations (1:5,000,000-1:30,000,000) were more or less hypersensitive. But the hypersensitiveness was not always absolutely specific. It did not manifest itself at all with phenol. Among the various formaldehyd concentrations, hypersensitization was effected by a formaldehyd content of the culture medium of 1:80-1:320,000. The reaction of the staphylococci to sublimate was of a similar nature; the highest sublimate concentration in which a culture could be raised usually produced resistance, while the lower concentrations (1:20,000,000 to 1:200,000,000 and even 1:2,000,000,000) produced hypersensitiveness. Staphylococcus cultures which were hypersensitive against sublimate were frequently also hypersensitive against silver nitrate, but not against phenol or optochin. This limitation of the specificity may be due to both substances being metallic salts. No satisfactory results could be obtained with dysentery bacilli and colon bacilli either in regard to hypersensitiveness or to resistance. Nor was it always possible to demonstrate the hypersensitiveness of those bacteria which were generally suitable for such experiments. In rare cases, hypersensitiveness could be demonstrated in culture passage with toxic mediums. Further experiments are necessary to clear up the relations between hypersensitiveness and habituation to poisons.

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**A Continuous Water Still for a Bacteriologic Laboratory.**

*Merlin L. Cooper, J. Lab. & Clin. Med., 8: 58, Oct., 1922.*

This continuous all glass water still was devised for use in a bacteriologic laboratory. Its advantages are that it utilizes only one source of water for both condensing and distilling, maintains a constant water level in the flask of boiling water by automatically feeding the flask with hot water as needed to replace the water evaporated, runs continuously with little attention, and has a capacity of 1 liter distilled water per hour for each flask in the system. A photograph is reproduced with a detailed description of the apparatus. •

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**Artifacts in Blood Culture Plates Simulating Colonies.**

*William Thalheimer, J. Lab. & Clin. Med., 8: 46, Oct., 1922.*

In a blood culture taken with a new Roux syringe, colony-like structures developed which simulated exactly colonies of *Streptococcus viridans*. Upon the new rubber plunger of the syringe there is a thin layer of yellowish powder, which probably contains sulphur. It occurred to the author that the fine particles of this powder might cause the phenomenon referred to. The pseudocolonies developed slowly, a

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few appearing in 24 hours, a moderate number in 48 hours, and all being present in 72 hours. Many colonies were taken from the plates, numerous smears from these were examined and many subcultures were made on a variety of mediums. In no instance was growth obtained in the subcultures nor were bacteria demonstrated in smears. The bouillon flasks remained sterile. To substantiate this finding, the scrapings of a new rubber plunger from a Roux syringe was cultured on blood agar. Colony-like structures identical with those described appeared in small numbers in 24 hours; in 48 hours, hundreds of these structures appeared. No bacteria could be demonstrated by smear or subculture. Many blood cultures have since been made with the original syringe after the powder on the surface had been thoroughly cleaned off and no colony-like artifacts have appeared in any of the plates.

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**The Bacteriology of Human Cystic Bile.**

*DeWayne G. Richey, Pennsylvania M. J., 26:4, Oct., 1922.*

The material for 408 specimens of human bile cultured routinely in the laboratory was submitted by surgeons at the time of cholecystostomy or recovered from the removed, intact gall-bladder shortly after operation. A positive culture was obtained in 208 cases (51%) from which 215 organisms were isolated, there being 7 instances where 2 different bacteria occurred in the same specimen. Of the 208 positive cultures, 35 were probably contaminators, leaving 44% as the incidence for pathogenic bacteria; 200 cultures (49%) were sterile. Ages of patients ranged from 15 to 69 years, 60% being equally divided between the fourth and fifth decades. There was nothing remarkable about the types of bacteria isolated, all readily falling into the ordained categories of well known organisms. *Bacillus coli communis* was encountered in 18% of positive cultures, and *B. coli communior* in 9%; *B. typhosus* in 7%; *B. paratyphosus* and *B. alkaligines fecalis* in 2% each. The members of the *B. mucosus capsulatus* group, including *B. lactis aërogenes*, *B. acidi lactici* and *B. Friedländer*, occurred in 25 instances, or 11%. *Staphylococcus aureus* had the same incidence as the typhoid bacillus (7%), while *Staphylococcus albus* appeared to be a pathogen in 3% of cases. *Streptococcus viridans* was found twice as frequently as hemolytic streptococci, the former being isolated in 12%, the latter in 6%. The presence of pneumococci was revealed in 3 cases, or 1.3%. The most important portals of entry of bacteria to the gall-bladder are the hematohepatogenous and the hematogenic, the former being the more frequent.

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**Bacterial Fermentation.**

*Fritz Mueller, Biochem. Ztschr., Berlin, 131:485, Sept. 16, 1922.*

Experiments were undertaken to supplement the influence of different nutritive solutions on fermentation by *Bacterium lactis aërogenes* by physicochemical methods, by the method of Michaelis and Marcora. All the static and dynamic properties characterizing the acidity conditions were determined, including (1) number of active hydrogen ions



determined by the gas chain or by suitable indicators; (2) neutral capacity, i.e. the amount of alkali or acid required to bring the solution to the neutral point or turning point of litmus tincture; (3) the equivalence capacity; (4) the buffer capacity of a solution, i.e. the resistance offered to a change of its acidity (pH) on the addition of acids (*S*) or of alkalis (*L*), exactly defined by the quotient  $dS : dpH$  or  $dL : dpH$ .

The effect of the addition of albumin and its catabolic products in increasing fermentation was especially studied. The influence of peptone on the fermentation of cane sugar and probably also on fermentation by other bacteria of the colon-aërogenes group, is due first to its characteristic as a nitrogen carrier and secondly to its buffer action. A solution of 1% peptone is quite enough to satisfy the nitrogen requirement; any further addition of peptone increases fermentation only by a buffer action and can be replaced equivalently only by phosphate and citrate mixtures. For other albumin substances (for example casein) the same is probably essentially true if only their physico-chemical constants are considered. The course of fermentation of a peptone-sugar solution inoculated with *Bacterium lactis aërogenes* is specially influenced by its H-ion concentration, less, but still noticeably, by the nature of the acids formed in fermentation, e.g. lactic or acetic acid; these act injuriously only as undissociated acids. The significance of the sugar concentration is closely connected with the buffer capacity of the nutritive solution. If this is slight in proportion to the sugar concentration, increase of the cane sugar content over 5% does not hasten fermentation. But if it is relatively great on inoculation, after an initial rise in acidity alkalization takes place.

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**Gonococci: Cultural Methods and Mutation.**

*L. Kandi, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:347, Sept. 25, 1922.*

Gonococci are very sensitive to influences of temperature and are capable of propagation only in temperatures ranging from 36° to 38° C. Ascites agar is the best culture medium; it is not prepared with bouillon but with an infusion of sheep's liver and sheep's spleen in equal proportions. On liquid culture mediums, a favorable growth was observed only if access was given to air. On ordinary agar, cultures may be obtained in the first generations, even without the presence of human protein, but they are not constant in the following generation. Laboratory strains frequently acquire the ability to grow on ordinary agar after passing through a series of transplantations on ascites mediums.

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**The Demonstration of Negri Bodies for the Diagnosis of Rabies.**

*Filippo Neri, Igiene mod., Genoa, 15:225, Aug., 1922.*

An experience of some years has enabled the author to improve the technic of the demonstration of Negri bodies with a special staining

process. The technic is as follows: Preparation of smears for fixation for 5-10 minutes in methyl alcohol or in absolute ethyl alcohol; fixation of small sections of Ammon's horn (about 3 mm.) in acetone or alcohol or, better yet, in Schaudinn's solution; attaching of sections of 5-7 $\mu$  to the cover-glass with distilled water, after the usual manipulations (xylol, absolute alcohol) and the necessary treatment with iodated alcohol for the sections fixed in Schaudinn's solution; from alcohol, direct removal to iodated eosin; 30 minutes' immersion for the smears and sections fixed in acetone or alcohol, 60 minutes' immersion for those fixed in Schaudinn's or Zenker's solution; careful washing in water; immersion in methylene-blue 1:1000, 15 minutes for the smears and sections fixed in acetone or alcohol, 45 minutes for those fixed in Schaudinn's or Zenker's solution and stained in aqueous iodated eosin; 30 minutes for those fixed in Schaudinn's or Zenker's solution and stained in alcoholic iodated eosin; washing in water; quick drying with paper. Differentiation is made in alkaline absolute ethyl alcohol (caustic soda 5:100,000) for smears and sections stained in alcoholic iodated eosin; in alkaline methyl alcohol (caustic soda 2.5:100,000) for smears and sections stained in aqueous iodated eosin. Then follow dehydration with alcohol, treating with xylol, and mounting with neutral Canada balsam or neutral Damar resin, or better, oil of cedar.

The special value of the method lies in the clearness with which the Negri bodies stand out, intensely colored by the eosin, against the blue of the cellular field and nucleus. They are differentiated from the erythrocytes, not only by form and position but also by the darker and more violaceous tint of the latter. Even extremely minute Negri bodies are brought out, which elude other methods. A colored plate illustrates the results.

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#### **The Classification of Streptococci.**

*J. Martin Beattie, J. State Med., London, 30:424, Oct., 1922.*

From the experimental side it seems clear that streptococci of human origin are not a unit, but that several types exist. In spite of much work done on differentiation of these types, success has been limited. Recently hemolytic properties and immunologic reactions have been largely employed. It may be accepted that the organisms of the type found in bronchopneumonia and influenza, which are specially pathogenetic, are hemolytic in their reaction. The high frequency of hemolytic streptococci in the human throat may explain the important rôle of these organisms as secondary invaders in numerous diseases. There is no doubt that streptococci play an important part in complications following infectious diseases, and that the hemolytic group is mainly responsible for these complications.

The importance of the nonhemolytic group must not be underrated. *S. viridans* has been recognized as the cause of ulcerative endocarditis. Much evidence has been put forward to show that non-hemolytic streptococci are causal of acute rheumatism and there cannot be any question but that endocarditis and arthritis of the rheumatic type can be produced in rabbits by intravenous injections of non-hemolytic streptococci isolated from cases of rheumatism. *S. rheumaticus*, with which the author has worked, differs from many of the

other nonhemolytic streptococci in its resistance to heat, its vitality outside of the body, and its retention of virulence. Rabbits given an intravenous injection of 0.5 c.c. saline emulsion (10 c.c. saline to feeble growth of 5 sloped agar tubes) of a culture which had not been inoculated for over 10 years, developed definite arthritis in 5 days and died in 10 days with marked endocarditis of the aortic valve. Agglutination, precipitation and absorption of agglutination tests have been tried, but the results are on the whole indefinite.

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**The Classification of Streptococci.**

*M. H. Gordon, J. State Med., London, 30:432, Oct., 1922.*

Although streptococci seem to be equally active as both primary and secondary infective agents, it is probably in the latter rôle that they cause the greatest damage to humanity. All streptococci investigated were isolated from actual disease processes and after being subcultured from a single colony, each strain was submitted to 3 routine tests: ability to hemolyze blood, to ferment raffinose and to ferment mannite. Sugars must be pure. By these 3 actions, which are completed within 48 hours, streptococci are resolved into 3 chief groups: pyogenes or hemolyticus, salivarius or viridans, and faecalis or enterococcus. The faecalis group is more resistant to heat than the others. Serologic study suggests that the streptococcus group includes a number of different races. Over 90% of the hemolytic streptococci encountered in ordinary hospital work appear to conform to the same serologic type. A large proportion of the strains of *S. faecalis* also belong to one type. Out of 24 specimens of *S. faecalis* investigated serologically, no less than 19, including all of the puerperal sepsis strains, conform to a single serologic type. The remaining 5 specimens appear to be serologically different from the preceding group, and from each other, as judged by the absorption of agglutinin test. In addition to these clearly defined races are numerous other serologically distinct groups to which, in the case of *S. salivarius* especially, there seems to be no end.

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**Differential Culture of the Streptococci.**

*H. Warren Crowe, J. State Med., London, 30:436, Oct., 1922.*

The medium demonstrated consists of defibrinated bullock's blood, mixed with peptone, or trypsin-agar, together with 1% glucose. In appearance it is opaque, chocolate colored and glossy. The medium is favorable for the growth of streptococci and on it the variations in character are very easily distinguished. A single focus of infection containing streptococci, when cultured on this medium, always shows a large number of varieties. In deciding on the streptococci which are found to grow, the color, opacity, and gross morphology of the colony must be considered. There are 7 groups distinguishable by color: (1) does not alter the medium at all, e.g. *S. hemolyticus*; (2) turns the medium black, e.g. *S. faecalis* of Andrews and Gordon; (3) turns medium black and also indents same, showing that the organisms digest

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the protein, the only member of this group being *S. zymogenes*; (4) turns the medium green just beneath the actual growth; (5) turns the medium green outside the colony and yellow beneath the colony; (6) has a narrow yellow ring around the colony; (7) has a wide yellow ring around the colony. One can distinguish 4 degrees of opacity and the gross morphology, that is the shape and size of various colonies, differs enormously.

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**Experimental Studies of the Nasopharyngeal Secretions from Influenza Patients. IX. The Recurrence of 1922.**

*Peter K. Olitsky and Frederick L. Gates, J. Exper. Med., 36:501, Nov. 1, 1922.*

The presence in New York City during the early months of 1922 of an acute respiratory infection, clinically resembling the epidemic influenza of 1918-19 and 1920, afforded the authors an opportunity to repeat and extend their studies of the nasopharyngeal secretions from influenza patients, which had resulted in the isolation of *Bacterium pneumosintes*. The nasopharyngeal secretions of 9 persons, who had within a few hours developed symptoms characteristic of the disease, were examined. The nasopharyngeal secretions of 8 other patients, obtained 6-36 hours after the onset of typical symptoms, were similarly studied. The washings from 1 of these patients stood at room temperature for 24 hours before transmission and cultivation experiments were undertaken. Both failed. Of the remaining 8 specimens, successful transmission experiments were initiated with 6. The seventh failed to induce the experimental disease in rabbits. The eighth specimen was only cultured after filtration through a Berkefeld candle and yielded a primary growth of *Bacterium pneumosintes* in an anaërobic ascitic fluid rabbit-kidney medium. The effects produced by the intratracheal injection into rabbits of these specimens of unfiltered nasopharyngeal secretions from influenza patients were identical with those observed during former epidemic waves.

Filtered nasopharyngeal secretions from each of the 9 influenza patients and from 10 other persons were inoculated into ascitic fluid and rabbit-kidney tubes under vaselin seal, and spread upon blood agar plates in an anaërobic jar. The lung tissues of affected rabbits were likewise cultured in the fluid medium, and sometimes smeared on anaërobic plates. By these methods cultures were obtained of strictly anaërobic, filter-passing, Gram negative organisms in material derived from 4 of the 6 influenza patients from whom an active agent had been transmitted to rabbits, from a seventh influenza patient whose nasopharyngeal washings were not injected into animals, and from 4 of 10 other patients not suffering from influenza. A survey of these microorganisms showed that *Bacterium pneumosintes* is not the only anaërobic, filter-passing, Gram negative organism to be found in the human respiratory tract. From 1 influenza patient and 4 of the non-influenzal controls which yielded positive cultures, other bacteria, not pathogenic for rabbits and not *Bacterium pneumosintes*, were obtained. There were identified as *Bacterium pneumosintes* the cultures derived from 3 of the 6 influenza patients, whose nasopharyngeal secretions

were pathogenic for rabbits, and from the seventh patient, whose secretions were not used in a transmission experiment. No cultures of *Bacterium pneumosintes* were obtained from the controls. The identification of the new strains of *Bacterium pneumosintes* was made on morphology, cultural characters, filterability, typical pathogenicity for rabbits, resistance to glycerol, reduction of resistance to secondary infection, and serologic and immunologic reactions. Numerous agglutination tests with the new strains against serum made with the old ones, and vice versa, have proved the antigenic identity of the new strains with the old, and among themselves.

Observations are reported of the presence of *Bacterium pneumosintes* in the lungs of infected rabbits. In microscopic sections stained by Giemsa's method, minute blue or violet stained bodies, morphologically identical with *Bacterium pneumosintes*, have been found repeatedly in scattered groups in the affected pulmonary tissues. Their usual site is deep in the ciliary margin of bronchial epithelium. Less often the bodies are found in mucous and serous exudate between the cilia and lumen of the bronchioles, where they are in the process of phagocytosis by polymorphonuclear cells and monocytes.

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**Studies in Respiratory Infections in Southern Australia.  
III. Pneumococcus and Other Members of the Viridans Group  
of Micrococci.**

*S. W. Patterson and F. E. Williams, J. Path. & Bacteriol., Edinburgh, 25: 450, Oct., 1922.*

During a research on the bacteriologic content of the lungs in a series of postmortem examinations of all patients dying in the Melbourne Hospital, a collection of strains of micrococci producing green coloration on blood-agar plates was made and submitted to further investigation. A second collection of these microorganisms was made from sputums of cases of acute respiratory infections in the wards of the hospital which were sent to the laboratories for report on the type of pneumococcus present. The authors' observations were made on a total of 271 strains. The group of micrococci here considered forms clear colonies on unheated blood-agar from 0.5 to 2 mm. in diameter, which are surrounded by a green halo with a diameter varying according to the age of the culture. The depths of the mediums are altered to green and become more translucent, but never transparent and clear as with hemolytic cocci. The colonies may be divided on their gross appearance into smooth or rough. The smooth colonies form a uniform emulsion in broth and the majority are agglutinated with a Type III pneumococcal serum. The rough colonies grow in fluffy or solid masses in broth and liquid mediums, cannot be emulsified on shaking, deposit quickly and leave a clear supernatant fluid.

The cocci insoluble in bile are of 2 kinds: (1) the rough granular green colony mentioned above as definitely streptococci; and (2) small round convex colonies having the characters of the smooth colonies already mentioned. The authors believe that the green micrococci may be divided by the bile test into pneumococci and streptococci. Of the pneumococci, Type I is distinct, Type III has as a counterpart the



*Streptococcus mucosus*, while Type II has affinities with a green streptococcus which is insoluble in bile and forms uniform emulsions in broth cultures (*S. viridans*). There is finally a type of streptococcus growing in granular lumpy colonies on solid and in liquid mediums (*S. granulosus*).

The data are presented in tabulated form.

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**The Lipin Content of Acid-Fast Bacilli.**

*Esmond R. Long and Leo K. Campbell, Am. Rev. Tuberc., 6:636, Oct., 1922.*

The authors examined 11 species of acid-fast bacilli and determined (a) the percentage of total lipin, extracted from the dry weight with petroleum ether after dehydration with hot alcohol, and (b) the percentage of wax (nonsaponifiable lipin) contained in the total lipin. These 2 values are represented by the 2 figures given for each species in the authors' table: H 37 human type tubercle bacillus 22.7, 77.1; B 1 bovine 22.3, 60.0; A 1 avian 11.0, 35.7; leprosy bacillus, Duval, 9.7, 27.2; turtle bacillus 36.3, 28.3; frog bacillus 37.1, 33.7; smegma bacillus 35.6, 4.6; dung bacillus 34.7, 5.4; grass bacillus 23.4, 9.4; grass III bacillus 30.3, 4.5; timothy bacillus 20.2, —. The high total lipin content of these acid-fast bacilli may be compared with the values ascertained for *Bacillus subtilis* (4.4) and *Staphylococcus albus* (2.8). It will be seen that, as regards the proportion of wax, the acid-fast bacilli fall into 3 groups (60-77%, 27-36%, and 4-10%, respectively).

Attention is called to Long's study of the nutritional requirements of the acid-fast group, and to the fact that the species investigated by him decrease in their glycerophilism approximately in the order in which they are listed above. The conclusion is that glycerol may be looked upon as a wax progenitor. This is also confirmed by Frouin's investigations. Another significant finding is that of the high wax content of the virulent forms. But the authors prefer not to stress this without further investigation of the disease-producing power of the so-called tubercle bacilli of cold-blooded animals.

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**Lipin-Protein in Relation to the Acid-Fastness of Bacteria.**

*Esmond R. Long, Am. Rev. Tuberc., 6:642, Oct., 1922.*

There are 2 principal explanations of the acid-fastness of bacteria: (1) Ehrlich's hypothesis that it is due to an envelope of low permeability (which would also explain the fact that the bacillus once stained cannot be decolorized like other bacteria by the use of 33% nitric acid or alcohol), and (2) that the acid-fastness is determined by the content of an acid-fast ester or esters of a solid alcohol of high molecular weight, i.e. the peculiar lipin in which the acid-fast microorganism is rich. There are 2 obstacles in the way of complete acceptance of this latter theory: (1) bacilli which have been dried and treated with fat solvents until 20-35% of their dry weight has been removed remain acid-fast; (2) bacilli from which no fat or lipin has

been removed can be rendered nonacid-fast by mechanical disintegration (grinding in a mortar or between glass slides) or by chemical means not involving the use of fat solvents (hydrochloric acid, etc.).

It seemed reasonable to Long to suppose that conflicting views might be harmonized by assuming that acid-fastness does not depend merely on the presence of an acid-fast wax, but to an even higher degree on the manner of its disposition in the cell protoplasm, i.e. on the presence of protein-lipin combinations or mixtures from which the lipin can be extracted only with difficulty. This union may be either chemical or a fine emulsion, each individual lipin droplet being enclosed within a protein film. To demonstrate this, he experimented with 8 bacilli of the acid-fast group. After 20-35% of the dry weight had been removed by alcohol and petroleum ether, the dry residue was treated with normal hydrochloric acid (3.6%) for 48 hours at 37° C., washed in water, dehydrated with alcohol and again bleached with petroleum ether. In this way it became possible to remove an additional quantity of lipin (1-8% of the dry weight), which had apparently been firmly bound to protein before the acid treatment. In the following survey, the first figure represents the dry weight percentage of lipin removed before acid treatment, and the second figure the additional quantity removed after acid treatment: H 37 human type tubercle bacillus 22.7, 7.8; B 1 bovine 22.3, 3.8; A 1 avian 11.0, 0.8; leprosy bacillus, Duval, 9.7, 4.1; turtle bacillus 36.3, 4.8; frog bacillus 37.1, 4.1; smegma bacillus 35.6, 2.3; grass bacillus 23.4, 2.3.

The lipin appears to be the same in all these microorganisms; it is probably a mixture containing the mykol of Tamura and mykol laurate. It is important to note the simultaneous disappearance, after acid treatment, of the acid-fastness and of the integrity of the bacterial cell, which had remained intact after the first removal of lipin. The non-acid-fast *Bacillus subtilis* was treated in the same way, and the results were identical in that 5.1% (of the dry weight) lipin could be removed after acid treatment in addition to the 4.4% removed previously; but this represents 50% of the total lipin, as compared with less than 30% in the case of the acid-fast bacteria. The finding of similar lipin-protein in *B. subtilis* requires the conception of a different manner of disposition in the 2 types of microorganisms.

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### **The Resistance of the Tubercle Bacillus to Boiling.**

*Karl Preis, Wien. klin. Wchnschr., 35:841, Oct. 26, 1922.*

All the other known acid-fast bacilli were completely decolorized in 1 minute by boiling water while tubercle bacilli still remained colored after 5 minutes. In carbolfuchsin the stain was displaced by equal amounts of sulphuric acid; on boiling over a flame the tubercle bacilli were decolorized and when they were stained again the acid-fastness was no longer present. If instead of sulphuric acid 5% carbolic acid was used, the bacilli also decolorized on boiling, but still showed acid-fastness when they were stained again, and also resisted cold acids. But if only water was used, the tubercle bacilli remained red on boiling, while all others were decolorized. The tubercle bacilli of cattle, birds and cold-blooded animals have much less resistance to boiling than the

human type. The author spread the material to be examined between slides and poured carbolfuchsin over it without any fixation. It was then heated for a minute until abundant vapor was given off, and after longer and stronger heating the color was more intense but the resistance to boiling was decreased. In comparative studies staining in a thermostat is recommended.

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**The Practical Application of the Precipitin Reaction in the Diagnosis of Pest and the Use of Agglutination to Identify Suspected Plague Bacilli.**

*Fulvio Pulgher, Igiene mod., Genoa, 15:193, July, 1922.*

Diagnosis of pest, easy in rats recently dead (buboes in 35% of the cases, containing bacilli in great quantities, congestion of the subcutaneous vessels with hemorrhages, often involving the internal organs also, enlargement of the spleen), is very difficult in rats in a state of putrefaction, in which the tissues have lost their characteristics and the bacilli have undergone various forms of involution difficult to recognize.

In these cases, only the precipitin reaction, discovered in 1913 by Piras, can render a diagnosis possible. It is a zonal reaction, which is obtained by placing an extract of the organs of the suspected rats (boiling for 5 minutes of the minced organs in physiologic solution and then filtering to obtain a perfectly clear liquid) on antipest serum: in case of positive reaction an opaque white ring forms at the point of contact of the 2 liquids. The author employed this test on the occasion of 2 epizootic outbreaks in Genoa; he used concentrated extracts obtained by adding to 1 part of the organs an equal part of physiologic solution. He found it useful to have ready in all cases the following controls: (1) antipest serum plus extract of test bacilli; (2) antipest serum plus extract of organs of normal rats; (3) antipest serum plus physiologic solution. He examined in this way 15 rats recently dead, and 20 dead rats in a state of advanced putrefaction. Of the first (in which the presence of the pest bacillus was also ascertained by direct investigation), 13 gave strongly positive reactions, 1 feebly positive, 1 doubtful; of the last, 10 gave strongly positive, 6, feebly positive, and 4, negative reactions. The reactions always occurred within the first 20 minutes; a reaction that occurred only after some hours would not be specific. Agglutination is a sure method of identification of suspected stock, if this is cultured at 20° C. It takes place after 16 hours at the surrounding temperature. To make identification of the bacilli more certain it is well to try the precipitin reaction with an extract of these.

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**Bacterioserologic Findings in Typhus.**

*M. Glusmann and L. Kandiba, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:337, Sept. 25, 1922.*

Plotz succeeded in raising on acid ascites mediums a bacillus which agglutinated with typhus serum in a dilution of 1:50,000 and showed  
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specific complement fixation after Bordet-Gengou's method in 71.8% of cases. He also succeeded in infecting guinea-pigs and in cultivating bacilli derived from these; he therefore regarded this bacillus as the causative agent of typhus. The authors inoculated guinea-pigs with the bacilli raised by this method and also performed prophylactic vaccination on human beings, with these results:

(1) In 63% of all typhus cases, an anaërobic bacillus is found which has been described by Plotz. (2) This bacillus cannot be cultivated by the methods of other authorities. (3) It does not cause typhus in guinea-pigs; it is not pathogenic for them nor apparently for other animals, e.g. rabbits. (4) It has not been found in other diseases. (5) Antibodies against Plotz's bacillus can be demonstrated in the blood of typhus convalescents by Bordet-Gengou's methods in 66-70% of cases. (6) The same antibodies are also found in human blood, apparently unrelated to typhus, in 40% of cases. (7) Plotz's bacillus would seem to suggest a mixed infection in typhus. (8) Thus far, no sufficient facts have been established to justify the identification of Plotz's bacillus with the causative agent of typhus. (9) The quantity of Plotz's bacilli and of their metabolic products contained in the blood of typhus patients is apparently very slight. (10) The inoculation with Plotz's bacilli is harmless, and it hardly seems to produce immunity against typhus.

## MYCOLOGY

(1d—264)

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### **Two Hyphomycetes Producing an Odor of Garlic.**

*Bartolomeo Bisbini, Ann. d'igiene, Rome, 32:757, Sept., 1922.*

Demonstration of the presence of arsenic by means of molds which, in the presence of this element, produce a garlicky odor, is of scientific and medicolegal importance. The most sensitive mold in this respect is *Penicillium brevicaulis*. The author has succeeded in isolating 2 other molds by exposing to the air Petri dishes with agar slightly acidified with tartaric acid and containing a solution of copper arsenate. The molds thus isolated are said to exert an action similar to that of *Penicillium glaucum*.

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### **Isolation of *Monilia Psilosis* in Tropical Sprue (*Psilosis*). Report of Case that Originated in Korea.**

*J. M. Rogers, J. A. M. A., 79:1677, Nov. 11, 1922.*

An organism which was identified as *Monilia psilosis* was isolated from the author's wife while she was suffering from undoubted and clinically active sprue (or psilosis) contracted in Korea. The organism was also isolated from the stool of the author who had been living for 4 years in the endemic area in a house in which, during 6 years, 5 cases of sprue had developed. He had also been in daily contact for 2 years with a case of sprue.

PARASITOLOGY

(1d—266)

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**A New Flagellate Parasitic in the Human Intestinal Canal.**

*G. C. Chatterjee, Indian J. M. Res., Calcutta, 10: 523, Oct., 1922.*

A flagellate furnished with 8 free flagellums was found in the stool of a child suffering from acute dysentery. The author considers this organism unique as no flagellates have yet been reported which possess more than 6 flagellums. A detailed description of this new flagellate is given.

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**Reversion of the Flagellate Form of *Leishmania Donovanii* and *Leishmania Tropica* to the Resistant Nonflagellate Torpedo and O Body in Culture Tubes and Its Bearing on the Attempts at the Search for the Transmitter.**

*R. Row, Indian J. M. Res., Calcutta, 10: 476, Oct., 1922.*

The presence of the resistant forms, or the O bodies, in the parasite *Leishmania donovani* determines the successful infection in a susceptible host. Even when the infecting material consists mainly of the flagellate stage of the parasite, no infection can be induced unless 3 or more injections of an old culture (consisting of a mixture of flagellates and resistant forms) are used, during what one would expect to be the incubation period, before the final dose is given. The flagellate forms are delicate and easily destroyed when in contact with fresh human serum; should the serum contain a few leukocytes, phagocytosis completes the destructive process; it is impossible to obtain a subculture from material subjected to this process. This being so, when one is in search of a transmitter, especially in case of blood-sucking insects, it is not so much the presence of flagellates as the abundance of the resistant O forms which counts. In view of these facts, the author takes exception to the assertion of Patton that the bedbug is the natural host of *Leishmania* and, therefore, a transmitter of kala-azar and oriental sore. Only the finding of resistant O forms in the bug capable of cultivation and causing infection on transmission could prove this assertion, and this, in the author's opinion, Patton has failed to do. The latter speaks of finding abundant flagellates in the gut of the bug after massive feeds of flagellates but does not say anything about resistant forms.

The author studied some of the conditions which in culture mediums lead to the return of the resistant forms of the *Leishmania* parasite. The study of the surface film growth in the vicinity of the level of the condensed fluid of the N.N.N. mediums reveal the following stages before the final return to the resistant forms becomes conspicuous: (1) This phase, lasting up to 2 weeks, marks the active division of very motile flagellates into flagellates of various sizes and shapes. (2) The shortening of the flagellums occurs, and though the elongated character of the flagellate is maintained, the differentiation of the body protoplasm has begun marking off the deep-blue staining



portion from the paler portion, the former becoming the resistant body, and the latter a thin membranous capsule (from 2-3 weeks). (3) The rudimentary stump of the flagellate disappears and condensation of the nucleus and the body protoplasm goes on side by side with the further approximation of the blepharoplast and the nucleus. The capsule is either cast off or is absorbed (4-5 weeks). (4) There is further shrinking of the protoplasm, the nucleus becoming compact and giving rise to the O bodies, oat-shaped forms of torpedoes indistinguishable from the parasites found in the lesions (5-6 weeks longer). The length of time necessary for the development of the O bodies essential to produce infection, precludes the assumption that the bedbug is the transmitter of the infection, unless it could be assumed that there is a third agency of insectiferous human pests who might take up the already multiplied flagellates and complete their developmental cycle, or take up the first host in the drying-up condition and thus act as an immediate transmitter. These considerations are only speculative and are put forth with all possible reservation.

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#### **An Experimental Study of Avian Malaria.**

*Etienne and Edmond Sargent, Arch. d. Inst. Pasteur de l'Afrique du Nord, Algiers, 2: 320, Sept., 1922.*

The parasite causing avian malaria is *Plasmodium relictum*. The authors have examined the effect of quinin upon this parasite. The protocols are given in detail. The dose of quinin required to destroy the parasites in a drop of infected blood is 0.075 mg., the blood being diluted by an equal volume of citrate solution. If the dilution be carried to one-eighth or one-sixteenth, the effective quantity of quinin also increases, reaching 0.2 mg. A single heavy injection of quinin destroys virulent sporozoites more readily than it kills the schizonts, if the sporozoites are artificially injected into the bird (canary). A large dose of quinin injected on the same day when the birds were bitten by infected mosquitoes did not affect the parasites.

The effect of injections of spleen, splenic extract, asaprol and cinchonized vertebrate blood upon *P. relictum* has been examined. Healthy canary spleen, injected a few days before inoculating the malarial parasite, attenuated the infection in 2 of 3 tests. Relative immunity was conferred in 1 of the 2 tests. In 5 of 7 tests, mouse spleen, similarly injected, did not affect the parasite. The infection was attenuated in the other 2 cases, in 1 of which relative immunity was produced. Dausse's splenic extract produced no effect. The injection of canary spleen, removed 2 days after inoculation with the parasites, produced infection in 2 of 3 tests. In 1 case the infection was mild, in the other severe but brief. Relative immunity was not produced in either case. Results were negative in the third test.

Asaprol was tested in 5% solution. The dose toxic for the canary is 0.05 mg. Birds intensely infected with *P. relictum* were less sensitive to asaprol than were normal birds, but sublethal doses of asaprol had no effect upon the parasites.

The cinchonized blood tested was obtained from canaries, mice,

guinea-pigs and pigeons, which had received an intraperitoneal injection of quinin. The undiluted blood was injected, subcutaneously and intraperitoneally, into infected canaries. No curative effect was produced in a total of 11 tests. In 11 preventive tests, 9 were negative; in 2 the infection was attenuated.

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**The Coördination of Biologic Data Referring to Malarial Parasites.**

*Ch. Vialatte, Arch. d. Inst. Pasteur de l'Afrique du Nord, Algiers, 2: 341, Sept., 1922.*

Among much confusing information concerning the several parasites of malaria, certain facts are well established. There are several morphologic types of Plasmodium. All gradations exist between the various species described. Some forms, such as the vivax and praecox, alternate seasonally. During maximum anopheline activity in all countries, a given type of Plasmodium predominates; during hibernation, mosquitoes lose all ability to infect. Cultures made in vitro may produce types different from those inoculated. The characters now serving to distinguish the several types are not at all fixed. Parasites infecting man do not infect other animals. Separation of the parasites into distinct species is not warranted. There is a correlation between the appearance of the praecox type and the period of the year during which anopheline activity is greatest. The different forms of the parasites represent adaptational stages. The protozoa have become adapted to a parasitic, intracellular life. Experiments should be made in this direction. Graphs and charts are given.

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**A Possible Fallacy in the Thick Film Method of Examination for Malarial Parasites.**

*J. A. Sinton, Indian J. M. Res., Calcutta, 10: 592, Oct., 1922.*

Sinton calls attention to the necessity of using freshly distilled water in making "thick film" smears in examination for malarial parasites. In the tropics, in hot weather, the water is easily contaminated with protozoa from the dust floating about. In the thick film method the dried films are covered with distilled water for 5 minutes to hemolyze the red cells; the smears, while still wet, are fixed in methyl alcohol, and any protozoa present in the distilled water can become entangled in the loose meshes of the fibrin, fixed by the methyl alcohol and stained in the later steps of the technic. The author cites such a case in his own experience when thick film smears showed positive forms while the thin films were negative for malarial parasites. The patients were receiving 30 gr. quinin daily, and the results were not in keeping with the previous findings. The fallacy was traced to the distilled water which became contaminated with flagellates. In the case of thin films distilled water is used only in final washing and the protozoa are not likely to become fixed to the film.

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**The Situation of the Malarial Parasite in Relation to the Red Blood-Corpuscle.**

*J. A. Sinton, Indian M. Gaz., Calcutta, 57:367, Oct., 1922.*

In view of the differences of opinion on this subject, Sinton undertook experiments to ascertain whether any more certain interpretation of the relative position of the malarial parasite and the red cell could be obtained. In the first series the blood was rendered hypotonic and in the second hypertonic. The blood was taken from patients with subtertian malarial infection showing parasites about 24-30 hours old. Many figures illustrate the variations in the relative position of the malarial parasite and the host cell under hypotonic and hypertonic conditions of the serum. These show extracellular forms, especially those found after hypotonic conditions, exactly similar to the extracellular forms depicted by Rowley-Lawson in 1918. The author agrees with Rowley-Lawson that in smearing the blood it would never be possible to reach the parasite if it were submerged beneath the surface of the red corpuscle, in order to pull or squeeze it out, without damaging the corpuscle beyond repair. In his preparations the cells which had extracellular parasites attached to them showed no such damage.

Experiments were also conducted with blood from a patient with malaria due to the benign tertian parasite, under both hypotonic and hypertonic conditions. Here also no interpretation could be placed on the findings other than that the parasites were extracellular, being for most of their asexual cycle attached to the outer surfaces of red blood-corpuscles.

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**The Biologic and Immunizing Relations between the Microorganism of Weil's Disease (*Spirochaeta Icterogenes*) and the Free Water Spirochetes (*Spirochaeta Pseudo-Icterogenes*).**

*P. Uhlenhuth and M. Zuelzer, Klin. Wchnschr., Berlin, 1:2124, Oct. 21, 1922.*

In the epidemiology of Weil's disease the transmission of the microorganism by rat's urine plays an important rôle. Infection of the water by rat's urine might also be responsible for bathing epidemics, though infection may be caused by the primary, initially saprophytic, occurrence of spirochetes in contaminated water. Spirochetes indistinguishable morphologically from the *Spirochaeta icterogenes* were detected by the authors in water from the most diverse sources. This *Spirochaeta pseudo-icterogenes* occurs frequently in organically contaminated surface waters and is less suitable for cultures, owing to the numerous accompanying bacteria, than the spirochetes found in slime plugs in the faucets of little used water supply systems. The latter were employed by the authors for biologic experiments. These experiments showed that the saprophytic water spirochetes, indistinguishable morphologically from *Spirochaeta icterogenes*, are capable of being so altered by addition and continuous transitions that they assume the latter's biologic characteristics and show the same serologic and immunizing properties. In one case they even became virulent to guinea-pigs who showed the typical picture of icterus. It is possible, therefore, that they may become patho-

genic to man under specially favorable conditions. The spirochetes of Weil's type possess very slight virulence. The diminished virulence of spirochetes excreted by man and rats is of particular epidemiologic significance and explains the slight danger of infection and the rare occurrence of Weil's disease in spite of the wide distribution of the spirochetes in free rats. The rat, which apparently derives the spirochetes from the water, probably represents the site at which the transition from saprophytism to parasitism takes place. The importance of the rat as a source of infection is evidenced by the large number of spirochetes excreted in the urine of this animal in at least 10% of the cases.

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**The Natural and Experimental Transmission of the Trypanosomiasis of Dromedaries by Stomoxys.**

*Edm. Sergent and A. Donatien, Arch. d. Inst. Pasteur de l'Afrique du Nord, Algiers, 2: 291, Sept., 1922.*

Trypanosomiasis is transmitted to dromedaries not only in rural places, but in shelters along their travel routes. Tabanids are the rural agents of transmission, Stomoxys the responsible agent in the shelters. A grave outbreak of trypanosomiasis occurred in an Algerian herd of dromedaries. The spread occurred from a single heavily infected animal. Extension does not necessarily occur from a chronically infected camel, only a certain slight degree of infection being required. Infection was proved not to occur from direct contact and to be produced at short distances and within a short time. It was not transmitted at a distance of 15 meters. The incubation period ranges from 3 to 11 days, the average being 5.

Stomoxys transmits the infection on the same day on which the infected animal is bitten. The principles enumerated were proved by experimental tests. The trypanosomes are deposited, during sucking, from the infected blood upon the exterior of the fly's proboscis and transmitted mechanically, and almost immediately, to a bitten healthy animal. The trypanosomes do not enter the fly's proboscis and have no developmental stage within the fly's tissues. In order that they may be deposited upon the proboscis, there must be bleeding from the sucking-wound made in the infected camel. The trypanosomes will die, and the secondary inoculation remain ineffective, unless the second animal be bitten very soon after the infected animal is sucked.

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**The Genera Bullinus and Physa in the Mediterranean Basin (Mollusca Pulmonata).**

*N. Annandale, Indian J. M. Res., Calcutta, 10: 482, Oct., 1922.*

All the forms of molluscs described by the author under the name Bullinus truncatus are capable of spreading the human parasite Schistosoma haematobium; on the other hand the species of Physa do not carry this infection. P. acuta and P. semiopaca are the only species of Physa that would be likely to be compared with Bullinus. Besides the difference in the shell and soft parts, there is also a difference in their habits;

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*B. truncatus* crawls slowly, while *P. acuta* moves very rapidly. *P. acuta* lives as a rule in clear running water, while *B. truncatus* lives in still or sluggish muddy water, often in ditches contaminated with sewage. *P. acuta* crawls openly on mud or stones while *B. truncatus* adheres to the lower surface of dead leaves, dirty pieces of paper, etc.

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**Hypoderma Crossii Sp. Nov., Parasitic in Its Larval Stages in Cattle and Goats in the Punjab.**

*W. S. Patton, Indian J. M. Res., Calcutta, 10: 573, Oct., 1922.*

A new species of Indian flies is described and named *Hypoderma crossii* (name of man who sent the larvas to the author). These flies are olive green in color, with gray, brown, and golden hairs. The larvas live in the skins of cattle and goats in the Punjab. The detailed description of the male and female fly is given. Nothing definite is known yet about the larval stages of *Hypoderma crossii*. The author thinks it possible that the female lays her eggs directly on the long hairs on the sides of the goats, that the larvas enter the skin and remain there, and that there is no migration to the esophagus and subcutaneous tissue as in the case of *H. bovis* and *H. lineata*.

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**The Presence of Phlebotomus Papatasi (Scop.) at Sedd-ul-Bahr.**

*G. Senevet and L. Parrot, Arch. d. Inst. Pasteur de l'Afrique du Nord, Algiers, 2: 419, Sept., 1922.*

Both *Phlebotomus perniciosus* and *P. papatasi* exist at Sedd-ul-Bahr. An extensive epidemic of "3-day fever" occurred among French troops stationed at Sedd-ul-Bahr in 1915. Certain authors have minimized the importance of *P. papatasi* in the transmission of 3-day fever. Due weight should be assigned to this agent of infection.

**1e. IMMUNOLOGY, SEROLOGY AND HEMATOLOGY**

(1e—315)

(1e—315)

**Natural Resistance and the Study of Normal Defense Mechanisms.**

*J. C. G. Ledingham, Lancet, London, 203: 898, Oct. 28, 1922.*

No one instance of normal immunity has yet been investigated as a complete problem. Partial mechanisms only have been studied. If a certain animal is immune to a particular experimental infection, such as anthrax, one ought to be able to explain fully what local phenomena have occurred to prevent a general invasion by the organism. To do so effectively must involve the testing of each possible mechanism separately and in conjunction, and it must involve a return to the cytologic study of the changes which the invading organism undergoes in situ. The problem must be attacked not only by methods which derive their authority from long experience with the bactericidal properties of cells and fluids, but also by methods which reflect the trend of present day



studies on general metabolism both of parasite and host. With regard to the former much has been made of the capsule, but the data on the point are contradictory. In every set of experiments strict attention must be paid to the maintenance of virulence. It may, indeed, be found that by experimental selection a test organism which has once proved virulent for one individual of a resistant species may prove equally so for all individuals of the species. Strains of *B. anthracis* have been selected which are alleged to have killed fowls, rats, and frogs, but the experiments lack confirmation.

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(1e—316)

(1e—316)

**Some Similarities and Dissimilarities between Plant and Animal Diseases, with Special Reference to Immunity and Virus Diseases.**

*V. H. Blackman, Brit. M. J., London, p. 718, Oct. 21, 1922.*

In plant pathology advances have been made, and numerous parasitic fungi and bacteria have been described, but knowledge of the physiologic basis of the resistance to disease of plants is still rudimentary. One difficulty is the great range in the degree of closeness of association between host and parasite. Penetration through uninjured surfaces plays a larger part in plant diseases than in animal diseases. With the parasite *Botrytis cinerea* the cuticular barrier is important in disease resistance. In one class of plant diseases there is a harmony between the physiologic processes of the parasite and host, leading to the symbiotic relationship—a necessary preliminary to the parasitic relationship. In another there is a disharmony between the physiologic processes, leading both to the death of the parasite and to that of the localized group of host cells, and thus to escape from disease. The case of *Botrytis* is an example of passive immunity; resistance depending on physiologic reaction of the plant may be termed active immunity. The plant pathologist is concerned with natural immunity, the physiologic basis of which in animals is still obscure. Acquired immunity resulting from one attack of a disease, and characteristic of many diseases of man, is quite unknown in relation to definite plant diseases. This is perhaps the most striking difference between plant and animal pathology. A point of contact is in the so-called virus diseases. Recently pathologists have become familiar with numerous definite, highly infectious plant diseases, in which all attempts to isolate a specific organism have proved of no avail—mosaic disease of tobacco, and leaf-roll of potato. These virus diseases show an interesting analogy with animal virus diseases in that plants are able to transmit the diseases without showing symptoms of them; such plants are thus of the nature of carriers.

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**Phagocytosis.**

*M. Nicolle and E. Césari, Ann. de l'Inst. Pasteur, Paris, 36:669, Oct., 1922.*

Inert or living particles may be taken up by mobile cells of invertebrates having no vascular system and by those of vascular and non-vascular tissues present in vertebrates. Phagocytosis occurs especially

in vascular tissues of the higher vertebrates. In congestive processes (catarrhs, edemas, etc.), it is subordinate; in abscess, granuloma, etc., it is a principal reaction. The leukocytes behave in various ways, but some are always destroyed, connective tissue proliferates and the mobile cells finally return to the circulation by inverse diapedesis. Pus is not a normal secretion. It constitutes an artificial culture medium. In infections, all gradations occur between the strictly local reaction and generalized conditions. Virulence must be estimated by a constant resistance, resistance by a constant virulence. Natural is explained by acquired resistance. Passive immunity is produced by the introduction of antibodies, active immunity is characterized by their formation. The site of this formation is unknown. Immunity includes that produced by disease, hereditary immunity, resistance to protozoa and immunity to large parasites. Immunity is not absolute and may be incomplete.

Immunity to bacteria and phagocytosis both depend on antibodies, but they are independent processes. Extracellular destruction of bacteria occurs, yet many organisms inhabit phagocytes and remain capable of killing the infected subject. Antitoxic immunity is not related to phagocytosis. The movements of free phagocytes depend on differences of surface tension, contacts, chemical processes, temperature, etc. Leukocytic movement and phagocytosis are inhibited by anesthetics sufficiently concentrated to coagulate protoplasm, favored by quantities just sufficient to lower surface tension and dissolve the external cellular lipoids. Phagocytosis includes adhesive contact, ingestion and digestion. Contact is difficult to examine; important information may be obtained by cinematographic methods. Particles may be ingested by active incorporation by the cell, or the cell may remain passive and the particle may merely enter the cell. If the particles are larger than a single cell, they may be surrounded by a number of cells which fuse and thus absorb the particles. In digestion of the absorbed particles, the process is the following. Antigens and antibodies mutually fix each other; complements separate and distribute the particles of the compound thus formed, which are then disintegrated by circulating proteolytic ferments. The process is essentially the same in extracellular and in intracellular digestion. It must be remembered that ingested organisms are not necessarily destroyed.

Phagocytosis represents heterologous agglutination. Homologous, or true, agglutination includes so-called spontaneous junction of similar cells, conjunction produced by normal serum and union due to antiserum. Either heterologous or homologous agglutination occurs when the cells or organisms concerned cease to remain in equilibrium with the surrounding medium. Specific antibodies may induce phagocytosis. They act upon the parasites, and not upon the phagocytes. Leukocytes of subjects immunized against a given bacterium are not more active than those of nonimmunized subjects. The toleration sometimes claimed to be undergone by leukocytes during vaccination is merely hypothetical. Complement, which reacts automatically within the bodily structure, is not essential for producing ingestion in tests made in vitro. Complements unite with antigens only by means of the antibodies, and never directly. Only traces of the antibodies are necessary. Bactericidal action may be started in  $2 \cdot 10^{-2}$  c.c. fresh normal guinea-pig serum by  $0.5 \times 10^{-18}$  c.c. antivibrio serum. Active substances present in normal humors and behaving like specific antibodies, may fix bacteria. The

latter, thus "sensitized," are ingested. The active substances are not resistant to temperature, but are not complements.

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**The Action of Ultraviolet Rays on Phagocytosis.**

*D. Albela, Deutsch. med. Wchnschr., Leipsic, 48:1347, Oct. 6, 1922.*

The author has studied the behavior of normal rabbit and guinea-pig phagocytosis toward staphylococci under the influence of quartz lamp irradiation. The irradiations were given from Jan. 1, 1922, to Jan. 29, 1922, 4 times a week for 30 minutes. The content of the serum in opsonins against *Staphylococcus pyogenes aureus* was examined before, during and after the treatment. The phagocytic figure during and after the treatment was subject to almost the same variations as in normal, nonirradiated animals. Therefore, in rabbits and guinea-pigs, irradiation with ultraviolet light has no decisive effect on the phagocytosis of staphylococci.

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**Elementary Bacteriophages of the Shiga Bacillus. (Concluded)**

*Oskar Bail, Wien. klin. Wchnschr., 35:743, 765, Sept. 21, 28, 1922.*

Very accurate, numerical results on the increase of bacteriophages can be obtained nicely in the following manner: A measured fractional part of the fluid, in which the increase of bacteriophages occurs together with the bacteria, is mixed with about 1-2 c.c. meat broth; this is heated for  $\frac{1}{2}$  hour to  $56^{\circ}$  C. and then mixed abundantly with the bacteria under investigation up to marked clouding, mixed with agar and poured into a plate. The resulting holes in the cloudy plate are counted like colonies of bacteria. Dilutions are made from the stock bacteriophagus and mixed with the culture of the bacteria to be tested and then streaked on an agar plate. Subsequently, the destruction of all or most of the grown bacteria is achieved by heating, so that those surviving no longer disturb the reaction, when a loopful of this preparation is streaked on a plate with a loopful of fresh broth culture of Shiga bacillus.

Both the bacteriophages  $\gamma$  and  $\gamma$  are true elementary bacteriophages. The bacteria-fast strains, the appearance and peculiarities of which may also serve for the recognition of bacterial reproduction, also behave similarly to alien bacteria in regard to the increase of bacteriophages achieved. In contrast to the great ease with which  $\gamma$ -bacteriophage leads to the development of variously fast strains,  $\gamma$ -bacteriophage cannot be used this way. It was more difficult to clarify the maze of the small elementary bacteriophage than to determine the large elementary bacteriophage of the Shiga bacillus, but even here a differentiation was usually possible: for example, it can be shown that bacteriophage "Watz  $\gamma$ " absolutely did not belong to the Shiga group but to the Flexner group. It should be emphasized that the decisive factor is not the ability of

increase, but the rapidity of increase. Among the true small Shiga bacteriophages should also be mentioned some which were present in the stool filtrates "Lauda," "Link" and "Dusch." The 2 stool filtrates "Ce" and "Eis" constitute a transition from the small bacteriophage to the described cloudy alien bacteriophage "Sab," "Dünger" and "Pok." Both form fast strains, which are resistant to their own bacteriophage but not to all other Shiga bacteriophages; these allow no increase of "Ce" and "Eis" in the usual experiment after 2 hours, but show a marked increase of "Krato g," "Krato k" and "Lauda k," and form no bacteriophages even in an unadulterated growth in meat broth. Those forms of bacteriophages are recognizable which as a result of their slight sphere of action are apparently restricted to the Shiga bacillus, but should preferably be considered as Shiga elementary bacteriophages because of their increase. On the other hand, those exceedingly numerous bacteriophages which do not belong to the Shiga group may be recognized with great certainty through the increase experiment, but these, as a result of their large sphere of action, may conjointly influence this organism.

That the bacteriophagic action is not caused by dissolved ferments but by physical particles is proved by the fact that on increasing dilution there is not a uniform weakening of the action on the whole plate culture, but that holes develop, the number of which decreases with increasing dilution. That the bacteriophage is not a filtrable virus or bacterial parasite (d'Herelle) is evidenced by the fact that in no medium does it increase in numbers independently, but that it only develops when the bacteria themselves are multiplying. In the multiplication of bacteria, as in all cells, a chromatin change in the nucleus plays the chief part. Then changes in the nonchromatin, vegetative part develop, first a dissolution and then a renewed building up. If the chromatin retains its capacity for dissolving but loses that for reconstructing the vegetative part, then in dividing, part of the nucleus remains doubled, but not surrounded by a vegetative membrane, and may act as a solvent on other bacteria in the process of reproduction. Thus new bacteriophages would be formed by the bacilli in the process of reproduction. If the loss of reconstructive capacity affects only certain special chromosomes (heterosomes), then the resulting bacillus, if capable of living at all, will lack that part which would have developed from the defective chromosome, e.g. the cilia. The bacteriophage then represents the transformed absent chromosome and cannot act on the altered bacillus. This explains the development of different bacteriophages from the same bacillus and of bacteriophage-resistant strains. The number of bacteriophages for one bacillus is limited by the number of chromosomes that are not necessary to life. Bacteriophages do not only dissolve and destroy the bacteria, but change their offspring. However, bacteria are sensitive to slight changes in structure, even of nonvital parts, and only a few survive the malformation. Therefore, destruction of the bacteria, which led to the discovery of bacteriophages, furnishes a ready explanation for bacterial mutations, including inherited resistance to bacteriophages. Two species of bacteria may be almost alike in chromatin structure, wherefore the action of bacteriophages may extend from one species to another. Close relationship or identity of one part of the inherited mass in 2 different bacteria explains why bacteriophages develop with a foreign bacillus. The new bacteriophage is not a descendant of the first, but its development is "induced" by the action of the first on the second bacterium.

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**The Typhoid Bacteriophagus.**

*J. Janzen and L. Wolff, Nederl. Tijdschr. v. Geneesk., Haarlem, 66: 1818, Oct. 21, 1922.*

The authors obtained the bacteriophagi from the stools of cured cases of typhoid. The technic required for studying the bacteriophagus is extremely important and contradictory findings have been reported chiefly because the methods were not precise. Cultures from the stools are incubated for 12-24 hours, then filtered, first through filter-paper covered with infusorial earth, then through a Berkefeld or Chamberland filter. Cultures of typhoid bacilli growing on agar are liquefied in island-like areas by the bacteriophagus. Beginners may find it difficult to develop the areas with a 1:10 dilution, but results are satisfactory with a 1:100,000 dilution. The bouillon culture of the bacilli must be prepared very carefully, otherwise turbidity may clear in 8 hours, only to be again produced by a secondary culture. Inhibition of the bacterial growth must be tested with various dilutions of the bacteriophagus. The latter may be prevented from growing by substances present in the stools. The island-like areas should appear in 24-48 hours; during the second 24 hours the cultures may be left at room temperature. The areas appear well on dry agar, but moisture renders them imperceptible. Suspensions should be made from young typhoid bacilli, transferred in a streak to the agar.

Twenty-eight strains of typhoid bacilli were examined, of which 6 resisted the bacteriophagi. Of the 6 resistant strains, 1 was obtained from a carrier cured 4 years before, another from a rapidly cured case. No serologic differences between the strains could be detected, all being agglutinated by specific serum. Four strains of bacteriophagi were employed. The results show that bacteriophagic races are quite distinct, no 2 behaving exactly alike. Individual characters are preserved and the authors could produce no variations. These characters are thus independent of the typhoid bacilli upon which the bacteriophagi are nourished. However, 2 strains inhibited the growth of *B. coli* as well as that of the typhoid bacilli. After acting on *B. coli*, the bacteriophagi no longer produced lysis of the typhoid bacilli. The process was reversed on again substituting typhoid for coli bacilli. In the original filtrate obtained from the stools in this case, the growth of the typhoid bacteriophagus was about 100 times as great as that of the bacteriophagus affecting *B. coli*. These results are not antagonistic to those reported by d'Herelle. Formation of the island-like areas is essential for studying the effects of the bacteriophagus. Their diameters vary from 0.5 to 5 mm. The size of the areas seems to depend on the strain of typhoid bacilli employed, or on the virulence of the bacteriophagus. The greater the virulence, the larger the area. In the authors' tests, it proved impossible to render the bacteriophagus capable of attacking naturally resistant strains of typhoid bacilli. Such strains absorb the bacteriophagus and render it powerless. Old bacteria, become resistant, may also absorb the bacteriophagus. If they can reproduce and thus form new young bacilli, the bacteriophagus again becomes active.

With resistant strains of bacilli, the bacteriophagic growth is usually slight during the first hour, increasing thereafter, thus showing that some of the bacilli are less resistant than others. A point is finally reached



where the remaining resistant bacilli prevent further bacteriophagic growth. The effect of infusoria upon the bacteriophagus is important in the epidemiology of typhoid. Thus far, the bacteriophagus seems specific for bacteria and is not affected by infusoria.

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**Historic Antecedents of Transmissible Microbian Lysis.**

*C. E. Pico, Rev. Asoc. méd. argentina (Biol. Sect.), Buenos Aires, 35:95, July-Aug., 1922.*

The author remarks that Emmerich and Low pointed out that in the stomach and intestines bacteriolytic enzymes play an important rôle in natural immunity, exerting an intense activity upon cultures of both the same and different bacteria. Naturally these authors did not consider that the indefinite transmissibility through passages in vitro had the importance later attributed to it by Twort and d'Herelle. But the so-called "problem of the 3 bodies" (bacterium, bacteriophage, and medium), which has become part of modern biology in accordance with d'Herelle's concept, has its equivalent in the works of these authors because of the bacterial interinfluences that are manifested not only in vitro but also in the human organism.

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**Is the Lytic Principle Contained in the Microörganisms?**

*C. E. Pico, Rev. Asoc. méd. argentina (Biol. Sect.), Buenos Aires, 35:99, July-Aug., 1922.*

A study of the diversity of the procedures by which transmissible lysis has been obtained leads to the doubt whether the internal mechanism of the process is always the same. Theoretically and a priori we can consider that for autolysis the bacteria must be in an unfavorable medium but one that does not alter their proper endogenous ferments. These conditions could be realized by the action of various substances, such as the different investigators have used. According to this interpretation all these substances would merely unloose the autolytic process, but the real agent responsible for the bacterial dissolution, which, continually regenerating, would permit of indefinite series, would be the endogenous ferments of the bacteria themselves. The author's experiments seem to point to this theory. He found that the action of pancreatin, papayotin, and ferments of leukocytes used by him for producing transmissible lysis, is at first relatively slow, but that when the initial lysis is once produced, it is transmitted rapidly through passages. He judged that pancreatin and papayotin act by unloosing transmissible lysis, from their behavior with respect to the so-called zones of lysis. If to a young culture of Shiga-Kruse bacilli in alkaline broth he added a certain amount of these ferments, and immediately placed a drop on an agar plate, he found after 24 hours of incubation that the culture had spread uniformly over the surface of the plate. If, however, he waited first till lysis had taken place, and then, mixing some drops of

the bacteriolized serum with an emulsion in broth of these bacilli, sowed a drop on the agar plate, he found after 24 hours an inhibition, total or partial, of the growth, according to the activity of the bacteriolized serum, but the phenomenon of zones of circumscribed lysis was faithfully reproduced. For success with these experiments, excessive quantity of bacteria in the culture must be avoided.

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**The Advantages of Single and Factional Dosage in Prophylactic Inoculation.**

*W. F. Harvey and K. R. K. Iyengar, Indian J. M. Res., Calcutta, 10:424, Oct., 1922.*

Fifteen pigeons were inoculated intravenously with a single dose of 1.5 c.c. of a prophylactic antigen for *Bacillus avisepticus*. Twelve days after that, they were tested with graduated doses of live *B. avisepticus* (from .000,000,005 to .000,000,5 mg.). Twelve of these pigeons died. Out of 15 pigeons treated the same way with a single dose of 1.5 c.c. of the vaccine and tested 19 days later, 11 died. Out of 15 pigeons treated with 2 instead of 1 dose of the antigen (first dose 0.5 c.c., second 1 c.c.) and tested 12 days later, 7 died. Out of 15 pigeons inoculated with 3 doses (0.5 c.c. each time) and tested 12 days later, only 1 died. All 58 untreated control pigeons inoculated with the same graduated doses of live *B. avisepticus* died. Thus 2 spaced doses of intravenous injection of prophylactic antigen in pigeons afford a better protection than a single dose, and 3 doses protect still better than 2. The production of agglutinins was greater with the divided doses than with a single injection of the same quantity.

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**Vaccination of Monkeys against Pneumococcus Type I Pneumonia by Means of Intratracheal Injection of Pneumococcus Type I Vaccine.**

*Russell L. Cecil and Gustav I. Steffen, Pub. Health. Rep. (U. S. P. H. S.), 37:2735, Nov. 3, 1922.*

In a previous study it was shown that monkeys can be completely immunized against pneumococcus Type I pneumonia by 3 subcutaneous injections of pneumococcus Type I vaccine. During the past 3 years a number of modified pneumococcus vaccines have been tried by the authors, but none of them has been quite so efficient as the original saline suspension of killed pneumococci. It seemed as if a satisfactory immunity might be obtained by injecting the vaccine directly into the trachea. The vaccine was similar in every respect to the saline vaccine employed in preceding experiments, and was prepared from a highly virulent strain of pneumococcus Type I. The neck of the animal was shaved, the skin painted with iodine and the vaccine injected directly into the trachea; immediately the operating board was elevated in order to facilitate the descent of the vaccine into the lungs. Injections were given at intervals of 5-7 days, the immunity of the monkeys being

tested 2-3 weeks after the third administration of vaccine by intratracheal inoculation with small doses of living virulent pneumococcus culture.

The object of the first experiment was to determine whether 3 large doses of pneumococcus vaccine would afford adequate immunity against a subsequent pneumonia. The 3 vaccinated monkeys remained perfectly well; and after being killed, the lungs were entirely normal and sterile. The control monkey developed typical pneumonia and pneumococcus Type I was recovered in cultures from the consolidated lobe. No protective substance could be demonstrated in any of the serums. A second experiment was carried out in which the total dosage of vaccine injected was equivalent to approximately one-tenth of the total dosage used in the first experiment. It was indicated that an adequate immunity can be established with the smaller dosage provided the vaccine is given intratracheally. There seemed some ground for hoping that a satisfactory immunity might be produced by the mere inhalation of a vaporized pneumococcus vaccine. Accordingly, 3 monkeys were sprayed every day for 3 weeks with pneumococcus vaccine, but they all developed pneumonia.

It was shown that immunity is more readily induced by the intratracheal route than by the subcutaneous. Failure to produce immunity by spraying of the throat may be due to the fact that the monkey, by closing off the nasopharynx, prevents the vaporized vaccine from entering the trachea. Immunity established by intratracheal injection is probably cellular in character.

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**A Method for Freeing Small-Pox Vaccine from Contaminating Bacteria.**

*H. Krumbach, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34: 477, Sept. 30, 1922.*

The small-pox vaccine marketed today is not usually free from contaminating bacteria, although it contains 80% of added glycerin and is stored in the refrigerator for a month. Several remedies for this condition are here described. Fornet's ether method renders the vaccine sterile, but animal experiments showed that treatment with ether for 24 hours rendered the vaccine avirulent, i.e. the ether process exerts quite a deleterious effect upon the vaccine, and the method is unsuitable for vaccination institutes. Attempts have, therefore, been made to achieve the same effect by the addition of disinfectants, using eucupinotoxin hydrochlorate 1:5000. When added to glycerinated vaccine in this proportion, it regularly frees the latter from contaminating bacteria in 7 days. The vaccine which has been rendered sterile by the addition of eucupinotoxin in this proportion, practically retains its virulence for at least 3-4 months. This has been proved by tests in human subjects, as well as in rabbits.

The addition of eucupinotoxin to vaccine in the proportion of 1:500 does not reduce its virulence after 1¾ month, as has been demonstrated by animal tests. In a concentration of 1:5000, eucupinotoxin destroys within 7 days all pathogenic organisms that may possibly contaminate vaccine, with the exception of the spore-bearing varieties. To

test this, anthrax and tetanus spores were used. A concentration of 1:500 positively kills anthrax spores in vaccine in 6 days, and tetanus spores in 8 days. Without glycerin, a concentration of 1-5000 of eucupinotoxin causes a transitory inhibition of growth. The cellular elements of the animal organism present in vaccine, combine with a considerable amount of eucupinotoxin. This combination cannot be dissolved by the subsequent addition of glycerin. Cell-free protein bodies also bind a great proportion of the eucupinotoxin. The disinfecting action of eucupinotoxin in solution diminishes gradually. In bulk it remains unaltered for at least 1½ year. As far as deductions from the number of tests here reported are justified, Kirstein's method of rendering small-pox vaccine free from contaminating organisms by means of eucupinotoxin, can be recommended.

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**The Routine Preparation of Diphtheria Toxin.**

*Percival Hartley and Olga Mary Hartley, J. Path. & Bacteriol., Edinburgh, 25:458, Oct., 1922.*

In the authors' method horse muscle, freed from fat and large vessels, was minced and weighed and for each preparation of medium 30-60 lb. minced muscle were used, soaked over night in tap water in a jacketed cauldron. Next morning, steam was passed through the jacketing until the temperature reached 95° C. This infusion, after cooling slightly, was filtered through paper pulp and the reaction of the clear filtrate adjusted to pH8. Then 2% Parke Davis bacteriologic peptone and 0.5% common salt were dissolved in the warm infusion and the reaction adjusted to pH. As containers, previously sterilized double Winchester bottles (capacity 5 liters) were used, 1 liter of medium being placed in each. For the sterilization of the medium steam was passed through the autoclave containing the Winchester bottles, for 1 hour, after which the pressure was raised to 10 lb. and maintained at this level for half an hour. After being in the incubator for 2 days 1 bottle was removed and the pH, total nitrogen, amino-nitrogen and proteose nitrogen determined. For the strain, Park-Williams No. 8 was used throughout. This was subcultured every 2 days on to "starter" bottles. The strain was also maintained on Loeffler slopes, subcultures being made every 14 days. Each preparation of medium was inoculated from 48 hours' old "starter" bottles, a piece of pellicle being carefully floated on to the surface of the fluid in each bottle. On this medium a thin but complete pellicle was generally formed at the end of 24 hours, but it was not quite uniform, small white islands or patches of thicker film being scattered over the surface. After 48 hours the film was thicker, firmer, and more uniform, and was found to be creeping up the sides of the bottle.

When liter quantities of medium were used the bottles were removed from the incubator after 7 days' growth. Prior to removal from the incubator, a smear was made of the growth in each bottle and examined. Then 0.5% pure carbolic acid was added and the sterilized culture was allowed to stand for at least 24 hours. Filtration was effected through paper pulp and the filtrates which failed to pass the sterility test were candled. For the determination of toxicity the intra-

cutaneous method described by Romer and Sames and developed by Glenny and Allen was used. The approximate value of the toxin having been ascertained, the minimum lethal dose was determined in the usual way. The reaction (pH) of each toxin was also determined.

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**Toxin and Reaction Changes Produced by the Diphtheria Bacillus in Culture.**

*Percival Hartley and Olga Mary Hartley, J. Path. & Bacteriol., Edinburgh, 25:468, Oct., 1922.*

In the authors' experiments cylindric-shaped bottles of 500 c.c. or 5000 c.c. were used as containers. The smaller bottles contained 100 c.c. of medium, the larger ones 1000 c.c. After inoculation, samples were withdrawn aseptically at the end of 1, 2, 3, 4, 5, 7, 9 and 11 days, a smear being made and examined for morphology, contaminations, etc. To each sample withdrawn 0.5% carbolic acid was added, and after standing for 24 hours in the dark the pH and toxicity were determined. From the data thus obtained, curves were plotted showing reaction change and toxin production during the course of each experiment. The intracutaneous method of Romer and Sames, as developed by Glenny and Allen, was used for determining toxicity. In the experiments described below, 410 separate tests were carried out to fix 99 points on 12 curves. Since 6-12 tests may be carried out on each guinea-pig the number of animals used was not excessive. The "skin test dose" or "L<sub>1</sub>/500-dose" was determined for each sample of toxin. This dose may be defined as the smallest volume of toxin which, when mixed with 1/500 of a unit of antitoxin, produces a typical positive reaction when injected intracutaneously into the shaven flank of a guinea-pig, the reading being taken about 40 hours after injection. The values thus obtained were used for plotting curves which are shown in charts.

In Experiment 1 the authors determined the reaction change and toxin produced by the same strain of *B. diphtheriae* (Park-Williams No. 8) when grown on mediums containing different varieties of peptone. The graphic results show the type of reaction curve to be the same in all 3 cases. The reaction curves for Parke Davis' bacteriologic peptone and difco proteose peptone are almost identical; the curve for Witte's peptone is of the same type and shape, but the values for pH are lower throughout. Experiment 2 was carried out in the same way as Experiment 1, except that the volume of broth inoculated was 10 times greater (1000 c.c.) than in the first experiment. The resulting data show the type of reaction curve to be of the same general character as in the previous experiment; the reaction changes occurred much more slowly, and the toxin production differed in the 3 cases. Experiment 3 was performed to study the reaction changes and toxin production which occur when different strains of *B. diphtheriae* are grown on the same medium under identical conditions. Here again the reaction curves are found to be almost identical while the toxin production varies with the 3 strains. In Experiment 4 liter quantities of mediums were inoculated, but all other conditions were the same as in Experiment 3. The results show that acid production as well as toxin production varied with the 3 strains.



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**The Value of Douglas' Medium for the Production of Diphtheria Toxin.**

*Percival Hartley, J. Path. & Bacteriol., Edinburgh, 25:479, Oct., 1922.*

Douglas has described a simple method for the preparation of nutrient broth, which consists in the digestion of ox muscle with trypsin for 2 or 3 hours. The mixture is then acidified with acetic acid and brought to a boil. Any undigested muscle is filtered off, salts are added to the filtrate and the reaction adjusted. The medium thus obtained is placed in suitable containers and sterilized.

Hartley has modified this method as follows: 150 gm. minced horse muscle are mixed with 250 c.c. tap water and heated to 80° C. in a steamer. Then 250 c.c. of 0.8% sodium carbonate solution (the anhydrous salt) are added and the mixture cooled to 45° C., after which 5 c.c. chloroform and 5 c.c. pancreatic extract (Cole and Onslow) are added. The mixture is incubated at 37° C. for 6 hours, the vessel being shaken at frequent intervals. Then 40 c.c. of normal hydrochloric acid are added, the mixture heated in a steamer for half an hour, and then cooled and filtered. The reaction of the filtrate is adjusted to pH8, and the medium distributed into containers before being put into the autoclave to be sterilized.

Definite quantities of the broth were placed in double Winchester quart bottles and all inoculated at the same time. At varying periods thereafter bottles were removed and toxicity tests carried out. The strain used was Park-Williams No. 8 and the toxicity of the samples was determined by the intracutaneous method of Romer and Sames and Glenny and Allen. The mediums thus prepared by a method similar to, and based upon, that of Douglas yielded diphtheria toxin on 29 occasions, the total volume obtained being 221.5 liters. Of this toxin about 72% had a minimum lethal dose of 0.0035 c.c. or less, and 28% had a minimum lethal dose which lay between 0.002 c.c. and 0.001 c.c. The use of horse flesh in place of beef or veal is not only a financial economy but is convenient since the horse muscle provides the protein cleavage products and the constituents of the meat infusion, both of which are essential for the elaboration of toxin. Toxin produced in this medium is stable, no deterioration being observed during prolonged incubation.

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**Surface Tension of Serum. IV. Action of Temperature.**

*P. Lecomte du Noüy, J. Exper. Med., 36:547, Nov. 1, 1922.*

The author shows the effect of prolonged heat at 55° C. on the initial value of surface tension of pure serum, and that of temperatures of 55°, 70°, and 100° C. on the time-drop of serum solutions. In the case of pure serum, only the initial value of the surface tension was measured, because the changes in time-drop would be almost of the order of magnitude allowed for experimental errors. Dog serum was kept in an incubator at 55° C. for 168 hours and measurements were made every 24 hours, according to a technic previously described. As the perturbations due to destruction of complement may be of such

magnitude that the presence of highly concentrated colloids would hinder their effect on surface tension, if there is any, experiments were carried out with solutions of serum. All solutions were made from the same serum, with 0.9% NaCl solution, especially prepared in clean vessels, the surface tension of which was 76.0 dynes  $\pm$  0.2 at 23° C. The solutions were stirred mechanically by an electric motor. The liquid was removed from the container during the stirring and poured into clean test-tubes. The heating was done in the following way: In most experiments 6 dilutions were prepared,  $10^{-1}$ ,  $10^{-2}$ ,  $10^{-3}$ ,  $10^{-4}$ ,  $10^{-5}$ , and  $10^{-6}$ . About 6 c.c. of each dilution were poured into 4 test-tubes which were prepared at the same time. One was kept at room temperature, 1 at 55° C. for 2 hours, 1 at 70° C. for 1 hour, and 1 at 100° C. for 5 minutes.

The observations made were these: The surface tension of pure serum, heated at 55° C., decreases progressively and regularly until the serum coagulates. A drop of 8.2 dynes was observed in 168 hours; the mean drop was 5.7 dynes in 120 hours and 4 dynes in 96 hours. The initial surface tension of solutions of serum at concentrations  $10^{-1}$ - $10^{-6}$  is practically not affected by heat, but the time-drop in 2 hours is modified. Each serum seems to react in its own particular way in regard to time-drop. However, there is a general tendency for the solution to show an increase of time-drop at the concentrations  $10^{-1}$ ,  $10^{-2}$ ,  $10^{-3}$ ,  $10^{-5}$ , and a decrease at  $10^{-4}$ , when heated at 55° C., a decrease of the time-drop at the concentrations  $10^{-1}$ ,  $10^{-2}$ , and  $10^{-3}$ , and an increase at  $10^{-4}$  when heated at 100° C. Only the changes observed below  $10^{-3}$  are constant in sign, in 75 or 80% of the cases. The concentration  $10^{-4}$  seems to correspond to a state of greater instability. This confirms the hypothesis of the existence of a monomolecular layer at that concentration, which was assumed on the basis of the existence of a maximum drop at  $10^{-4}$ . Should this be true, and provided the principle of Gibbs could be transformed so as to be applicable to mixed solutions of colloids and crystalloids, an idea of the size, or at least of one of the dimensions of the molecules or group molecules composing the serum could probably be obtained.

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**The Pharmacology of Blood Serum. Remarks on Handovsky's Article.**

*Hermann Freund, Klin. Wchnschr., Berlin, 1:2092, Oct. 14, 1922.*

The author takes exception to some points in Handovsky's article (SURVEY, Nov., 1922, 1e—272). Physical as well as chemical conditions may be concerned in the pharmacologic effects of defibrinated blood. The first effect might consist in a chemical alteration, namely an increase in decomposition products from cellular disintegration, with alteration of the cell and serum colloids; or the colloids might undergo a primary physical change, with increase in the globulin fraction and secondary decomposition products. Handovsky has shown that purely physical changes reinforce the vasoconstrictor effect of the serum. Further, Handovsky also maintains, contrary to other authors, that the vasoconstrictor effect is not dialyzable and that the vasoconstrictor effect of the serum is confined to the albumin fraction. This view is opposed

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by the author. As the effects of the serum show great similarity to those of biogenetic amines, the author attributes serum activity to active substances, although the chemical definition of these substances is still lacking.

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**The Pharmacology of Blood Serum. Answer to Freund.**

*Hans Handovsky, Klin. Wchnschr., Berlin, 1:2093, Oct. 14, 1922.*

The author suggests that the phenomena involved herein should be regarded as collochemical ones. It is still an open question whether the altered activity of the blood or serum is conditioned by chemically detectable substances, possibly biogenic amines, or by altered colloidal behavior of the blood plasma. In regard to the second possibility the author assumes disturbances of equilibrium in the blood (which represents a composite colloid), that condition alteration of the blood plasma. For instance, the blood colloids' water-combining capacity, or the relative proportions of albuminous substances, or the amount of lipoids, may be altered. Possibly both factors, chemical and physical, participate in the blood plasma's action.

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**The Combination of Hofmeister's Anion Series and the Action of Heat as a Reaction for Plasma Lability.**

*Géza von Gerlőczy, Klin. Wchnschr., Berlin, 1:2134, Oct. 21, 1922.*

Hitherto only the protein fractionation method has been employed to determine the degree of plasma lability, which is produced by shifting of the protein quotient and which indicates the amount and extent of cellular destruction. Inasmuch as subjective factors are associated with this method, the author has worked out a method to show whether flocculation does or does not take place. He endeavored to produce a different precipitation by employing various reagents. For this purpose, he selected Hofmeister's series and supported the salt action by the effect of heat in the water-bath. No flocculation whatsoever could be detected in normal plasmas during heating. In the case of plasmas strongly sensitive to salt a coarse, massive flocculation is observed in all flasks when heated to 52-53°. Here, the protein quotient is displaced strongly toward the coarsely dispersed, labile protein fractions and proceeds parallel to cellular disintegration and to the inflammatory process. Such coarsely flocculent protein precipitate is observed with all members of the series in true pulmonary tuberculosis, in disintegrating malignant neoplasms, in parenchymatous kidney disease and in all exudative processes. In another group the precipitation is absent in the last or the last two members; the temperature is generally 53-54°. The reaction takes place in this manner in active apical pulmonary processes with tendency to improvement, syphilis and arteriosclerosis with destruction of tissue, and the labile plasma of pregnancy. In a further group, precipitation takes place in a constantly decreasing number of Hofmeister's series, demands an even higher temperature, and the flakes

become smaller and finer. Such reaction in tuberculosis of the lungs indicates a favorable prognosis. The method may be also used for controlling the efficacy of a given treatment. A reaction series becoming constantly more complete indicates bad prognosis. However, in the resorption of large exudates, coarse disperse amounts of protein enter the blood; the preponderance of the latter is manifested by diminished stability which in this case does not signify a bad prognosis. The various protein fractions with their different degrees of hydration take part in this reaction. The course of the reaction is parallel, on the one hand, with the saturated sodium chlorid precipitation and the rapidity of sedimentation of blood corpuscles and, on the other, with the serum lability reaction. It thus shows the importance of fibrinogen in the above mentioned diseases, at least in the sense of changing the dispersity through increase in fibrinogen.

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**A Critical Investigation of the Freund-Kaminer Reaction.**

*Louis Herly, J. Cancer Res., 6:337, Oct., 1921.*

In connection with determining the value of Freund-Kaminer reaction (normal serum destroys cancer cells, while serum of cancerous persons has no lytic effect), the author also retested the observation of Kraus and v. Graff to the effect that serum obtained from rabbits and guinea-pigs acts like normal serum in destroying cancer cells, whereas the serum of rats, goats, and sheep has no lytic effect on the same cancer cells. The tumor used, by the author in these experiments, was the Flexner-Jobling rat carcinoma. A fine emulsion of the healthy margin of the tumor, free from connective tissue, was added to rabbits, guinea-pigs and rat serums, in proportion 1:6, and incubated for 3 hours at 37° C. At the end of this time, the treated tumor particles were inoculated into a series of rats. The results obtained did not agree with those of Kraus and v. Graff, there being an even percentage of takes in the 2 series of rats—those inoculated with cancer cells previously treated with the rabbit, guinea-pig and rat serums, and those with untreated cancer cells, used as controls. The author adds that rabbit and guinea-pig serums may have a different action on human cells, but have no damaging action on the cells of a transplanted rat carcinoma.

Freund and Kaminer method was modified in the following points: cells from rapidly growing rat carcinomata were suspended in the serum of normal rats, and in the serum of rats bearing this tumor without intervention of any extraneous substances, such as NaCl, or NaFl (used by Freund and Kaminer); after incubation for 3 hours the cancer cells treated with both normal and cancerous rat serums were inoculated into a series of rats. The objection to Freund and Kaminer procedure was that the latter used tumors (obtained at autopsies) that had been in the mortuary or the laboratory for indefinite periods of time, and it is questionable what proportion of the cancer cells so used were alive; the serum was obtained sometimes fresh, sometimes postmortem, in which case it might have been decomposed. The author realizes that the serum of an animal with a transplanted tumor may not be the same as that of one with a spontaneous neoplasm. Nevertheless, it can be shown whether normal serum damages the tumor cells; if it does

not, the distinction between the serum of a normal animal and one with a spontaneous tumor vanishes.

The author's findings do not agree with those of Freund and Kaminer. There was no marked difference in the results of inoculation whether tumor serum or normal serum was used. The conclusion is, therefore, that the value of the Freund-Kaminer reaction remains, at present, unproved in so far that normal rat serum has no deleterious effect on the cells of Flexner-Jobling rat carcinoma.

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**A Study in the Diagnosis of Cancer by Means of Serum Reaction.**

*J. A. Shaw-MacKenzie, Lancet, London, 203:759, Oct. 7, 1922.*

The author has previously shown the occurrence, in disease, of variations in the accelerating power of serum on lipase, as contained in pancreatic extracts or in the juice itself. This power of the serum is decreased in cancer but on improvement or recovery returns to normal or is increased. Although the reaction occurs in conditions other than cancer, such as tuberculosis, it has enabled a diagnosis of cancer to be made. Absence of the reaction is an aid in excluding the presence of cancer. A saponified extract or an ether extract of cancer tissue is added to serum of patients suffering from cancer, and when the mixture is incubated for a given time at 37° C. a permanent emulsion or precipitation appears in the serum. This so far has not occurred in the serum of normal persons. The ether extract was generally used and the serum diluted with pure sodium chlorid solution (0.85%) in the proportion of 2-3 parts of saline to 1 part of serum. The saponified extract has the advantage of removing after incubation any initial cloudiness in normal serum, unless the cloudiness is too great. Diabetic serum has given trouble because of the initial milky character. Results of the test vary from opacity, cloudiness or trace with sometimes a ring at the junctions of the fluids in carcinoma serum. Serums in 61 cases were examined with positive results in all cases of malignant disease (31); all cases of different pathologic conditions other than cancer (25) gave negative results. All normal cases examined gave negative results except one. The reason for the positive result obtained in this case on 3 different occasions could not be determined. The help given by this test in making diagnosis of cancer was very striking. The total number of serums examined was 136, including 58 normal. In 41 cases a previous positive or negative diagnosis was confirmed, and in 35 cases in which no details of the case were known, or the diagnosis was uncertain, a correct diagnosis was made, as confirmed subsequently.

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**The Serologic Relationships of the Paracholera Vibrios to Vibrio Cholerae, and the Serologic Races of the Paracholera Group.**

*T. J. Mackie, Brit. J. Exper. Path., London, 3:231, Oct., 1922.*

The question of serologic races of *Vibrio cholerae* was studied by Douglas in 1921, who investigated a number of strains from different



sources and also certain noncholera vibrios, including strains of *V. paracholerae* A and B. Douglas concluded that *V. cholerae* represented one serologic race and embraced also the hemolytic varieties (corresponding to the El Tor vibrio), conclusions also reached by Mackie in the course of certain studies of *V. cholerae* and other intestinal vibrios in Egypt. Douglas, using formolized broth cultures as emulsions for the agglutination tests (according to Dreyer's method), and incubating at 50°-55° C. for 2 hours, found that, after continued subculture on artificial medium, *V. paracholerae* A acquired the property of being agglutinated by anticholera serums, though without a corresponding result in absorption tests. Douglas also found that in the case of emulsions prepared in plain salt solution, and incubating at 50°-55° C., *V. cholerae* serum agglutinated *V. paracholerae* A and B; the results with known strains of *V. cholerae* were somewhat irregular. The marked differences between plain and formolized emulsions as indicated by Douglas seemed to Mackie to be a factor of the greatest importance in agglutination technic so the opportunity was taken for retesting certain paracholera strains with an antiserum to a *V. cholerae* (Egyptian origin), especially as these strains had been continuously cultivated on artificial medium for a period of 4-5 years. The agglutinating serum to *V. cholerae* was prepared in the usual way and tested with the homologous strain and a *V. paracholerae* A strain "G." Careful comparisons were made between the results obtained when the tests were carried out by different methods. Different agglutination emulsions were compared: (1) plain saline emulsions from 18-24 hour agar slope cultures; (2) saline emulsions formolized, 0.1% formalin; (3) formolized broth emulsions prepared by Dreyer's method. Further comparisons were also made between results obtained after incubation at 37° C. and 55° C. for 2 hours, and readings were taken after the test mixtures had been standing at room temperature overnight following removal from the incubator. The author's tabulated results show that the paracholera vibrios comprise a group which is not serologically homogeneous, but which, in addition to *V. paracholerae* A and B, represents a considerable number of serologic races precisely differentiated by agglutination reactions. By direct agglutination tests, using plain saline emulsions and incubating at 37° C. for 2 hours, the paracholera vibrios are distinctly differentiated from *V. cholerae*. *V. cholerae* antiserum exhibits apparent coagglutination under certain conditions toward *V. paracholerae* A and certain similar types; this effect develops more slowly than the agglutination of the homologous organism and is of lesser degree and of lower end-titer; it is most markedly elicited when formol-broth emulsions are used and the tubes are incubated first at 55° C.

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#### **Hemolysins and Antihemolysins of Cholera-Producing and Noncholera-Producing Vibrios.**

*Francesco Maria Marras, Ann. d'igiene, Rome, 32: 752, Sept., 1922.*

In order to determine the effects of mediums and time on the production of hemolysins on the part of cholera-producing and noncholera-producing vibrios, as well as the reaction of filtrates of cultures of such microorganisms in the presence of blood of various

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species of animals, the author cultivated several strains of both kinds of vibrios in peptonized water and in broth for 24-72 hours, and filtered the cultures through a Chamberlain filter; he then mixed 1 c.c. of the filtrate with 1 c.c. of a 2.5% suspension of human, bovine, sheep's, dog's and rabbit's red cells. The test-tubes were kept in a thermostat for 4 hours, then in the ice-box for 24 hours.

The experiments showed that hemolysins are formed against red blood-cells of various animal species in cultures of both noncholera-producing and cholera-producing vibrios; the test of positive or negative hemolysin formation is thus not adapted, notwithstanding the statement of some authors, to a differentiation of the 2 types of vibrios. The hemolysins formed are resistant to heat, withstanding even 60° C. for one-half hour. Inoculation of filtrates of either cholera-producing or noncholera-producing vibrio cultures (3 c.c. injected 4 times at 7 day intervals) produces in animals (rabbits) a serum possessing anti-hemolytic properties. The latter antihemolysins are capable of inhibiting hemolysis by filtrates of vibrio cultures; they are specific, which explains their action only in the presence of homologous filtrates.

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**Clinical and Serologic Behavior of Bacillus Paratyphosus B Breslau.**

*Holm and F. H. Lewy, Ztschr. f. Hyg. u. Infektionskr., Berlin, 96:288, Sept. 25, 1922.*

The authors have studied 2 cases of paratyphoid infection. One case presented the aspects of typhoid, the other of meat-poisoning, but in both bacilli of the Breslau group were isolated. On the basis of these 2 cases, the authors have sought to investigate the clinical, bacteriologic and serologic relations of the two varieties of the Bacillus paratyphosus B. The organisms cultivated from the 2 cases proved to be completely identical with the Breslau organism cultivated by Bitter in his mackerel epidemic, inasmuch as all 3 precipitated each other mutually. The clinical aspect of one of the cases was that of typical typhoid with a 2 weeks' course, an amphibolic stage and a slight relapse. The other patient, who had partaken of mackerel, suffered only from acute gastro-enteritis, from which he completely recovered in 3 days. The so-called food-poisoners of the paratyphoid B group must be regarded as identical as far as their serologic behavior is concerned, no matter to what clinical course they may give rise; but they are much less closely related to Schottmüller's variety than to each other. Although it is true that all serums agglutinate all the paratyphoid B group, even to the final titer with one exception, the saturation experiment showed that the receptor apparatus must possess a certain independence in both directions.

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**The Serology of Scarlet Fever.**

*Karl Pesch and E. Thomas, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34:502, Sept. 30, 1922.*

The Wassermann and the Meinicke tests were performed to learn the reason for a positive result of the complement fixation reaction in

scarlatina. Forty-two serums of children suffering from scarlet fever were tested. Among 150 specimens of serum from 50 scarlet fever patients, 36 gave a positive, 15 a doubtful, 99 a negative Wassermann. The Meinicke reaction was negative in all 150 serums. Relations appear to exist between the first and second attack of scarlatina, and a positive result of the complement fixation reaction. No relation exists between the result of the reaction and the kind of extract used. Positive results are less frequently obtained with extracts from scarlet fever organs, than with syphilitic liver extracts. The outcome of the reaction is markedly dependent upon the strength of the extract and the accuracy of adjusting the complement. Probably a number of factors work together to produce a positive result of the complement fixation test in scarlet fever (fever, cell destruction). Accepting the spirochete nature of the organism of scarlet fever, the possibility of a group reaction in spirochetoses must be borne in mind (syphilis, frambesia, Weil's disease, scarlet fever).

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**Studies on the Biology of Streptococcus. II. Antigenic Relationships between Strains of Streptococcus Hemolyticus Isolated from Scarlet Fever.**

*Walter Parks Bliss, J. Exper. Med., 36:575, Nov. 1, 1922.*

In a previous publication, the author set forth the results of a study of the agglutination reactions of 25 strains of Streptococcus hemolyticus isolated from the throats of patients suffering from scarlet fever. Of these strains, 20 were agglutinated at equal titers by 4 separate immune serums prepared by immunizing rabbits to individual strains of scarlatinal streptococci. With the exception of 4 strains, none was agglutinated by any of 4 antistreptococcic serums obtained by immunizing animals to strains of Streptococcus hemolyticus isolated from diseases other than scarlet fever. These facts suggest that certain hemolytic streptococci found in the throats of scarlet fever patients constitute a single biologic group.

The following facts, confirmatory of this statement, are brought out in this article. Hemolytic streptococci have been found in 100% of the throats of patients with scarlet fever during the first week of the disease. The average length of time that these organisms are present in the throat varies from 10 to 20 days. No morphologic or cultural characteristics peculiar to the hemolytic streptococcus from scarlet fever can be demonstrated. Each of 10 immune serums prepared from different strains of scarlet fever streptococci agglutinated more than 80% of the strains isolated from scarlatinal throats. On the other hand, scarlatinal streptococci are not agglutinated by immune serums prepared from hemolytic streptococci isolated from other pathologic sources. Serum from patients convalescent from scarlet fever agglutinates weakly or not at all the homologous strain of hemolytic streptococcus. The specificity of the agglutination reaction of scarlatinal streptococci is confirmed by absorption experiments. Scarlatinal antistreptococcic serum affords some degree of protection against virulent scarlet fever streptococci but has no protective power against hemolytic streptococci from other diseases. In a small epidemic of scarlet fever a healthy

carrier of hemolytic streptococcus was detected; the organism carried was identical in its serologic reactions with strains of hemolytic streptococci isolated from active-cases of scarlet fever. In a study of a number of contacts, in only 1 instance was a scarlatinal type of hemolytic streptococcus recovered from the throat.

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**On the Antitryptic Action of the Blood.**

*E. Beaton, Brit. J. Exper. Path., London, 3:224, Oct., 1922.*

The view of antitryptic action which appears to prevail at present is that the reduction of tryptic action produced by serum is due to a diversion of the enzyme from the added substrate by the proteins of the serum, these proteins being assumed to be themselves acted upon by trypsin only slowly and with difficulty, but to be able to adsorb the enzyme and so to diminish its effective concentration. The method employed by the author for the determination of the antitryptic power of the serum constitutes practically a titration of the inhibitory factor against the trypsin. Graduated dilutions of the trypsin solution are mixed with uniform quantities of the serum under examination; a suitable substrate is then added, incubation maintained for a fixed period, and the result read by noting the presence or absence of an observable degree of digestion in the tubes. As a substrate the author found a 1% solution of caseinogen to be most satisfactory.

Tabulated observations note (1) the antitryptic power of the protein fractions of serums having different inhibitory capacities; (2) the relation of the antitryptic power to the quantity of albumin and of globulin in the serum; (3) the relation of the antitryptic power of the serum-albumin to the quantity of albumin in the serum. The data thus recorded show that the albumin-fraction of the serum-proteins is more antitryptic than the globulin-fraction, and that in human serum the inhibiting factor lies almost entirely in the former. There is no proportional relation between the antitryptic power of the serum and the concentration, either of the total protein or of the albumin; but on the contrary, an increased inhibitory capacity may be accompanied by a diminished protein content, and especially by a diminished albumin content. The author says the antitryptic power of the serum cannot be conceived as due to a simple diversion of the enzyme by the protein as such, but must be dependent upon some at present unrecognized character of this protein.

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**Action of Antigen on Fibroblasts in Vitro. II.**

*Albert Fischer, J. Exper. Med., 36:535, Nov. 1, 1922.*

Fischer reports further experiments showing the influence of antigen concentration on the process of immunization of fibroblasts in vitro.

Dog serums and human ascitic fluid were used as antigen. The antigen was added to chick embryo juice in such proportion that 1 volume of the mixture and 1 volume of chicken plasma would give the desired concentration. The experiments were carried out by taking a fragment of tissue from a 10 year old strain of fibroblasts and dividing it into 2 equal parts. One was cultivated in a medium with antigen;

the other was placed in a medium without antigen and served as control. After 48 hours' incubation, the experimental and control cultures were divided into 2 parts. One-half the experimental culture was transferred to a fresh medium with antigen, and one-half the control culture to a fresh medium without antigen. The remaining halves of the experimental and control cultures were placed in a medium containing the antigen under a high concentration (50-66%), which had a marked inhibiting action on the growth of normal tissues. In this way it was possible to ascertain the resistance gained by the immunized tissue at a given time during the experiment. The quotient of the rate of growth of the experimental subculture (immunized strain in the high concentration of antigen) divided by the rate of growth of the control subculture (nonimmunized strain in the high concentration of antigen) expresses the degree of immunization.

The toxic effect of ascitic fluid upon fibroblasts was slight, while that of dog serum was marked. When a small amount of antigen (1.5-2% dog serum, or 8% ascitic fluid) was present in the medium, the resistance of the fibroblasts slowly increased, reached its maximum after about 14 days, and then gradually decreased. The curve expressing the phenomenon closely resembles that of Jörgensen and Madsen showing the production of antibodies in an animal which received daily injections of antigen. When the antigen was present in the medium in a high concentration (5-8% dog serum), the resistance reached its maximum in 4 days, and decreased rapidly.

The author concludes that in the immunization of fibroblasts in vitro against a foreign protein, there is a relation between the amount of antigen, the time of the appearance of immunization, and its duration. When a small amount of antigen is used, immunization slowly reaches its maximum, and slowly decreases. When a large amount of antigen is used, immunization reaches its maximum in a short time, but the protection is of equally short duration.

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#### **The Origin and Nature of Bacteriolytic Diastases.**

*R. Turro, J. de physiol. et de path. gén., Paris, 20: 376, July-Sept., 1922.*

The author's former work has clearly demonstrated the presence of diastases in cells of the liver, spleen, kidney, lung, thyroid, lymphatics and intestinal mucosa. His present method of obtaining cellular ferments consists of triturating in a mortar, dehydrating with acetone, filtering, drying in vacuo and finely pulverizing. To 1 gm. of the powder, mixed with 20 c.c. saline solution (1:100), is added 40-50 drops chloroform. The mixture is vigorously agitated for 15 minutes, then incubated for 12 hours at 40° C., then centrifugated and decanted or filtered. The liquid is as clear as water and actively lytic with various bacteria. The ferments cease to appear after the 12 hour incubation. This procedure gives more active ferments than those obtained by maceration or by the methods of Buchner or Gengou.

Extracts thus obtained from pleural or peritoneal exudates are more active than those obtained from pus. Ferments have also been



obtained from mutton, nervous tissue, and pancreas. They are all actively lytic for *Bacillus anthracis* and other bacteria. Heating at 40° C. for 12 hours destroys their activity, which is lost in 6 hours if the ferments are acting upon bacteria. Air and light do not inactivate. The ferments seem to be fixed by bacteria and in this condition continue lytic activity for some time after the extract itself is no longer active. Fixed ferments do not redissolve in saline solution. The activity is not altered by heating for 1 hour at 55° C. but boiling destroys it. Bacilli resist the ferments in varying degree. The optimum temperature lies between 40° and 45°. The powder containing the ferments loses some of its activity 6 hours after drying, remains stationary for the following 6-8 days and becomes notably less active after the tenth day. Up to this day, but not later, feeble extracts may be reactivated by adding fresh extracts.

Ferments are not specific for bacteria as such, but for the chemical substances composing the bacteria. Their actions are proteolytic, amylolytic and lipolytic, whether they are intracellular or extracellular. Leukocytic ferments behave like those in the circulating serum. Ignorance of the composition of complex glucosids, polypeptids, etc., is apt to be lost sight of. The reactions occurring during the splitting of proteins, fats and carbohydrates are unknown. If the theory of bacteriolysis by ferments is accepted, fixation by alexin becomes an unnecessary explanation. Ehrlich's theory is also valueless. Antigens are digested as foods are digested. Certain ferments may be termed bacteriolytic, but their reaction with chemical groups, and not with separate bacterial species, should be borne in mind.

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**Observations on a Bacteriolytic Substance ("Lysozyme")  
Found in Secretions and Tissues.**

*Alexander Fleming and V. D. Allison, Brit. J. Exper. Path., London, 3:252, Oct., 1922.*

The authors give the name "lysozyme" to a bacteriolytic substance present in most of the secretions and tissues of man and other animals and in some vegetable tissues, and having properties similar to those of ferments. In the authors' experiments they employed cultures of a large nonpathogenic coccus (which they called *M. lysodeikticus*), as this coccus was particularly susceptible to the action of lysozyme, and furnished a convenient indicator for work in connection with its distribution and properties. This indicator microorganism revealed lysozyme to be present in greatest amounts in such secretions as tears, nasal mucus, and sputum; in the tissues, especially cartilage; and in very large amount in egg-white. Lysozyme is very stable, retaining its activity in a fluid medium at room temperature for several months. It acts equally on dead and living microorganisms; is especially active toward some nonpathogenic bacteria; and in all probability is the cause of such bacteria being nonpathogenic, the authors think. The action of lysozyme is manifest at temperatures between 4° C. and 65° C., but it is slower at the lower temperatures. It is not destroyed by long contact with the common organic solvents.

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**The Antibactericidal Properties of Colloidal Silica.**

*S. L. Cummins, Brit. J. Exper. Path., London, 3:237, Oct., 1922.*

From previous work on the antibactericidal action of the bile salts in connection with the culture of *Bacillus typhosus*, the author concluded that bile owes its power of assisting the growth of typhoid bacilli in blood cultures to its power of inhibiting the action of complement. It appeared probable to the author that this anticomplementary action of bile and the bile salts was attributable to their colloidal characters when in solution or when their solutions were mixed with body fluids, so to further the study a supply of colloidal silica was obtained. A 24 hour broth culture of *B. typhosus* was diluted with sterile normal saline as follows: (a) 1:100, (b) 1:1000, (c) 1:10,000, (d) 1:100,000, (e) 1:1,000,000. Two series of Dreyer's tubes, each 5 in number, were prepared, so that in each series each tube contained a similar amount of fresh, active blood, together with a measured volume of typhoid emulsion in which the number of bacilli diminished in tenths; the only difference being that in Series A, there was no silica colloid but only a volume of distilled water, while in Series B each tube contained a volume of silica colloid. Both series were now placed in the incubator at 37° C. for 1 hr. 40 min. They were then withdrawn and from each tube, after shaking, a measured volume was abstracted and added to the surface of an agar slope, the agar cultures being numbered, in each series, from 1 to 5. These agar cultures were then incubated over night and the growths examined. In series A there was normal bactericidal activity, as shown by the almost complete destruction of typhoid bacilli within the space of 1 hr. 40 min., while in Series B the presence of the silica colloid was sufficient to preserve the bacteria from the action of the blood.

To determine whether this "antibactericidal" action of silica colloid was due to interference with the action of "complement" the author prepared 2 series of test-tubes, each series consisting of 5 tubes. Into each tube of Series A was placed 0.1 c.c. 5% suspension of sensitized red blood cells, normal salt solution, and a varying amount of complement. Into each tube of Series B was placed 0.1 c.c. 5% suspension of sensitized red blood cells, normal salt solution, 0.1 c.c. silica colloid with 0.8% sodium chlorid, and a varying amount of complement. The amount of hemolysis occurring in Series A (without silica varied from a trace to nearly complete, while in Series B (with silica) hemolysis did not occur at all, clearly indicating that the action of the "complement" had been inhibited by the addition of silica colloid to the mixture.

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**The Constitution of Isogenetic and Heterogenetic Sheep Blood Hemolysins and Their Antigens. Studies on Hemolysins. III.**

*Fritz von Gutfeld, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34: 524, Sept. 30, 1922.*

The author studied some theoretic questions attaching to the characteristics of Forssmann's hemolysins and those produced by injections  
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of sheep blood, and their antigens. He employed immune serums obtained by injecting rabbits and guinea-pigs with fresh sheep blood and sheep adrenals (heterogenetic). Sheep blood, beef blood and guinea-pig organs were used as antigens (material carrying receptors). By means of fixation tests he studied the question of whether an identity or a difference exists between the receptors of the various antigens among themselves and the antibodies produced by them. These experiments have shown: That the isogenetic immune serum, obtained by injecting rabbits with fresh sheep blood, in addition to the isophilic amboceptors usually contains a greater or less considerable amount of heterophilic amboceptors, which can be removed by treating the immune serum with organs of a heterogenetic type or with boiled sheep blood. A purely isophilic sheep-blood immune serum (free from heterophilic and beef-blood amboceptors) is obtained by injecting guinea-pigs with fresh sheep blood.

From purely isophilic or heterophilic antiserums fresh sheep blood binds considerably more heterophilic amboceptors than isophilic. In these tests no difference in avidity could be shown. Sheep blood saturated with isophilic amboceptor is still able to combine with heterophilic amboceptor, but when saturated with heterophilic amboceptor, it can no longer take up the isophilic. In a mixture containing large amounts of heterophilic amboceptor together with a small quantity of isophilic, it is possible to demonstrate quantitatively the isophilic amboceptor after the heterophilic amboceptor has been taken up. Lipoid albumin complexes, the biologic behavior of which is discussed in the paper, form the substratum for the antibody-binding and antibody-forming functions of sheep blood-corpuscles and of guinea-pig organs.

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**Acid Hemolysis and the Effect of Calcium upon It.**

*Adolf Jarisch, Biochem. Ztschr., Berlin, 131:547, Sept. 16, 1922.*

Calcium works antagonistically to acids. The effect of calcium on acid hemolysis was studied. In these experiments with increasing amounts of acid in a solution containing calcium, a point is reached at which, hemolysis having been brought about at a certain concentration of acid, there develops with the next higher amount of acid a zone of inhibition in which brown blood corpuscles are precipitated from a colorless solution. These blood-corpuscles do not dissolve under the action of hemolytics; they seem therefore to be fixed and show ultramicroscopic coagulation of their contents. The cause of this coagulation may be acid precipitation and the fact that the different constituents of the blood-corpuscle—the stroma albumin, lipoids and the product of acid decomposition of the hemoglobin—have widely different iso-electric constants and therefore at certain hydrogen-ion concentrations take opposite charges and precipitate one another. The coagulation of blood-corpuscle substances under the influence of acids can be demonstrated to a slight degree also in calcium-free solutions, but the presence of calcium strengthens the process as it prevents the premature exit of hemoglobin and therefore causes the pigment to take part in the precipitation inside the blood corpuscle. In this action calcium can be replaced only by strontium, barium and magnesium. The

iso-electric point of the stroma albumin as well as of the intact blood-corpuscle is found at a different place with the use of different regulators, and this explains the contradictory reports in the literature. The precipitation optimum of the stroma substance in dissolved blood as well as the cataphoretic turning point in intact blood-corpuscles is found in acetate and lactate mixtures at about pH 5, in phosphate mixtures at about pH 3.2. The electric charge of the blood-corpuscle can be determined by capillarization. Anodal blood spreads out on the filter paper in drops, cathodal blood clings to the fibers.

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**Hemolysis by Morphin and Its Homologues.**

*Heinrich Rhode, Biochem. Ztschr., Berlin, 131: 560, Sept. 16, 1922.*

In earlier studies it was shown that codein phosphate in isotonic concentration does not cause hemolysis but that morphin chlorid and dionin have a strong hemolytic action. This observation gave rise to a systematic testing of different salts of morphin and related drugs. In order to limit as far as possible the part taken by the alkaloids and the anions combined with them, solutions of the different salts in different concentrations were brought into contact with blood corpuscles which were floated in solutions of 0.9% salt solution, 0.4% sodium sulphate, 8.5% cane sugar, 5.4% dextrose or mannite. From these experiments it was found that: (1) Morphin and its methyl, ethyl and benzyl derivatives hemolyze as chlorids blood corpuscles washed in sodium chlorid in increasing degree; bromid, sulphate and phosphate act more weakly. (2) Washing of the blood corpuscles with cane sugar weakens the effect of all the above named alkaloids, the weakening greatly increasing in the following order: morphin, codein, dionin, so that under these conditions the effectiveness of the 3 chlorids increases in the reverse order, that is from dionin to morphin. (3) Hemolysis by ammonium salts shows analogous differences in cane sugar and sodium chlorid blood corpuscles. (4) Sugar blood corpuscles of hogs seem to have a smaller volume than sodium chlorid blood corpuscles.

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**The Periodic Opacity of Wassermann Antigen in Progressively Increasing Concentrations of Sodium Chlorid.**

*J. Holker, J. Path & Bacteriol., Edinburgh, 25: 522, Oct., 1922.*

In previous experimental work the author has shown that, when a mixture of serum and Wassermann "antigen" is treated in a certain way with progressively increasing concentrations of sodium chlorid, ranging up to 10%, it exhibits a periodic variation of opacity. When serum without antigen is similarly treated, the periodic opacity phenomenon is still more marked. When, however, Wassermann antigen without serum is thus treated, the periodic opacity is not exhibited.

It was thought probable that the Wassermann antigen would also exhibit the periodic phenomenon if the concentration of sodium chlorid was increased beyond 10%. Accordingly experiments were extended

to include concentrations of added sodium chlorid ranging up to a saturated solution. The heart extract used was an acetone-insoluble one, prepared from a calf's heart by the method described by Bordet and Ruelens (1919), and was cholesterinized by the addition of an equal volume of a 1% solution of cholesterin in absolute alcohol. Into each of a series of resistance glass test-tubes was pipetted 0.5 c.c. antigen, and to this was then added rapidly 49.5 c.c. solution sodium chlorid which progressively increased in concentration in each successive test-tube. The resulting suspension was then placed in the thermostat at 40° C. for 4 hrs., shaken initially and every hour afterwards. At the end of that time the opacity of the suspension was determined by means of the No. III. type of apparatus recently described by Holker. The opacity of the suspension was then plotted against the concentration of the sodium chlorid. Other concentrations of antigen were similarly treated with sodium chlorid and the results recorded graphically. A method of measuring the periodicity of these curves was found to be the ratio between the amplitude and the length of the period. A complete oscillation was taken to be that part of the curve lying between 2 successive minima. The amplitude of the oscillation was expressed in degrees of opacity and was taken to be the length of the perpendicular dropped from the maximum to the line drawn through the 2 minima. The length of the oscillation was expressed as the difference in the normality of the net amount of added sodium chlorid at the minima. The ratio of the amplitude to the length of the period was termed the characterizing ratio of the period.

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**Preservation of Complement Serum with 25 Per Cent Sodium Chlorid.**

*M. W. Lyon, Jr., and Vera B. Trager, J. Lab. & Clin. Med., 8: 48, Oct., 1922.*

The preservation of complement serum with sodium chlorid has been advocated by many workers. The accepted method is the addition of 17% sodium chlorid and keeping the serum cold. It occurred to the authors that a greater quantity of sodium chlorid might be more effective and that the higher dilution required to make the solution of complement and salt isotonic would not require the addition of so much, if any, isotonic salt solution in complement fixation tests to make a satisfactory bulk for the reagents used. Apparently the largest amount of sodium chlorid that serum can hold in solution is 25%. One cubic centimeter of complement serum containing this amount of salt diluted to 30 c.c. yields a 1:30 dilution of complement in an isotonic salt solution. Complement serum preserved in this way, and kept on ice, retains its activity for hemolysis with specific amboceptor with comparatively little change for 3-4 weeks and is satisfactory for performing the Wassermann test. At room temperature this salted serum retains its activity for about 10 days. Bacteria can exist in serum saturated with sodium chlorid even though such serum is kept on ice. It is probable that the presence of bacteria in preserved complement serum is a factor in its deterioration.



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**The Practical Value of an Ice-Water Bath for Use in the Complement Fixation Test for Syphilis.**

*H. Virginia Langworthy and E. Jane Kerley, J. Lab. & Clin. Med., 8: 54, Oct., 1922.*

The authors aim to show the practical value of an ice-water bath for use in laboratories not equipped with a brine-cooled cold room. The range of temperature of an ordinary ice-box is between 11° and 16° C. and may approach 18° C. if the ice-box is opened too frequently. An ice water-bath can be kept at a temperature as low as 2° C. Brine-cooled ice-box temperature (3°-6° C.), ordinary ice-box temperature (12° C.), ice water-bath temperature 2° C.) and room temperature (20° C.) were used to test a limited number of serums received for the Wassermann test.

Comparing the fixation in the ice water-bath and brine-cooled ice-box, the difference is slight. Six, or less than 10% of the entire number tested with the plain alcoholic antigen, and 3, or less than 5% of the number tested with cholesterinized antigen, gave greater fixation at 2° than at 3°-6° C. The difference in fixation between the ice water-bath and ordinary ice-box temperature is more marked. Twenty-nine, or 40% of the number tested with plain alcoholic antigen, and 6, or 10% of the number tested with cholesterinized antigen, reacted more strongly at 2° than at 12° C. The difference in fixation between ice water-bath and room temperature was much more pronounced. Forty-seven, or 66%, of the specimens tested with plain alcoholic antigen, and 12, or 20%, of those tested with cholesterinized antigen, gave greater fixation at 2° than at 20° C.

A household ice-box could be easily converted into an ice water-bath. A wooden one lined with zinc having the inside measurements 12 x 17 x 12 in. is sold for \$13.00. The outlet pipe of such an ice-box could be stoppered, the space under the shelf nearly filled with ice, and sufficient water added to cover the wire shelf to a depth of 1½ in. Such a water-bath should keep a temperature of 2° or below for 4 hrs. or longer, and should prove of great practical value where a brine-cooled room is not available.

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**Some Light on the Nature of the Substances Responsible for Complement Fixation in Tuberculosis.**

*R. W. Hodge, Pub. Health J., Toronto, 13: 442, Oct., 1922.*

While working with serums of tuberculous patients, it became necessary to note the effect of (a) removal of lipoids and (b) precipitation of globulins on certain serum reactions.

*Lipoids in Tuberculous Serum Reactions.*—It is evident from even an incomplete review of the literature that lipoids have a not inconsiderable influence on the Wassermann reaction, that the lipoidal content of certain animal serums favors conditions for the development of nonspecific fixation and, finally, that the lipoidal content of most tuberculous serums is higher than normal. The work so far has been

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an attempt to show in what way the lipoidal content of tuberculous serums is related to the complement fixation in tuberculosis.

In extracting the lipoids from the serum as completely as possible and noting the effect of this removal on the reactions under examination Friedemann and Herzfeld's method, slightly modified, was used. Serum (0.5 c.c.) was spread on filter paper and dried in an electric oven at 45° C. for an hour. One volume dried in this way was reserved for a control; to the other volume in a test-tube was added a mixture of equal parts absolute alcohol, ether and chloroform. The tubes were shaken half an hour, after which the mixture was poured off and the filter paper dried at 37° C. Saline was then added to the dried filter paper to make a dilution of 1:5, the filter paper was worked into a pulp, the liquid pressed out, poured into another tube and centrifugalized to remove the particles of filter paper. The control portion of the serum was treated in the same way except that the extraction with alcohol, chloroform and ether was omitted. By this method of extraction, 15 tuberculous serums, showing various degrees of fixation from weakly positive to very strongly positive, were tested. The degree of fixation given by the extracted serum was compared with (1) that given by the untreated serum and (2) with that given by the dried and redissolved serum.

Results in the control untreated fraction (dilution 1:10) and in the control dried fraction (dilution 1:5) were quite comparable, there being only a moderate loss of fixation bodies in the latter. The dried and extracted serums, however, in almost every instance showed a marked loss of power of fixation, in many cases complete.

*Proteins in Tuberculous Serum Reactions.*—The relationship of proteins to complement fixation has not been definitely determined. In the work under consideration euglobulin was precipitated by bubbling carbon dioxid through serum diluted 1:10 with distilled water till a heavy turbidity developed. The serums were allowed to stand for 2 hours till a flocculent precipitate was formed; they were then centrifugalized. The supernatant fluid was poured off and rendered isotonic. The precipitate was redissolved in saline to give the original 1:10 dilution.

The results were definite and uniform. The fixation bodies in the supernatant fluid are in practically the same concentration as in the untreated serum. There is only an occasional and slight amount of fixation in the euglobulin fraction.

Renaux's experiment with syphilitic serums was repeated with the same result as that obtained by him and a comparable phenomenon was demonstrated in tuberculous serums. Methyl alcohol extract of the tubercle bacillus was the antigen chosen. When this is added to such a serum and the euglobulin is precipitated, it is found that the fixation bodies are transferred from the supernatant fluid to the sediment. When, however, syphilitic antigen or alcohol-ether extract of the tubercle bacillus is added to such a serum before the euglobulin is precipitated, no alteration in the normal distribution of the fixation bodies occurs. It seems likely then that the lipoidal antigen in each case is carried down with the euglobulin sediment and that it pulls down the corresponding fixation bodies in combination.

*Discussion.*—The evidence presented indicates that the fixation bodies in human tuberculous serums are lipoidal in character because:

(a) Extraction of dried human sera with alcohol, chloroform and ether removes or destroys these bodies almost completely. (b) When the serums are dried on filter paper and redissolved in saline there is only a moderate loss of fixation power. This indicates that the active substances redissolve quite readily; protein does not redissolve readily after drying. (c) Fixation bodies occur only irregularly in the euglobulin fraction of the serum; they occur in the supernatant fluid in the same concentration as in the untreated serum.

The author's observations which appear, at first sight, to be opposed to those of Nishida and Petroff and also of Kapsenberg, have shown that complete precipitation of fixation bodies in syphilitic serums is not necessarily accompanied by complete precipitation of globulin as almost complete precipitation of syphilitic fixation bodies is obtained when lipoidal emulsion (Wassermann antigen) is added to the diluted serum before the precipitation of euglobulin by carbon dioxid. In this experiment only the euglobulin is precipitated; the sediment is not increased in amount and the remaining globulin fraction can be demonstrated in the supernatant fluid by half saturation with ammonium sulphate. It is evident, then, that the fixation bodies in syphilitic serums are not globulins, but are merely carried down with the globulin fraction when it is completely precipitated. It seems altogether likely that precipitation of the tuberculous complement fixation bodies in the globulin sediment obtained with ammonium sulphate is of a similar nature.

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#### **Defective Feeding.**

*S. Racchiusa, Haematologica, Naples, 3:478, Sept., 1922.*

The author fed some guinea-pigs on cabbage, potatoes, corn and bran, while other animals were kept fasting. In the fasting animals there was no change in alexin; on the other hand, in animals that had been subjected to poor or deficient nutrition there were more or less marked changes in the amount of alexin, dependent upon the extent of alimentary deficiency. In the great majority of cases there was a diminution in the amount of alexin, increasing progressively and reaching considerable proportions during the last week of the animal's life.

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#### **Amboceptors and Receptors. II.**

*J. Morgenroth and R. Bieling, Biochem. Ztschr., Berlin, 131: 525, Sept. 16, 1922.*

Through the heterologous hemolysins a series of antigen relationships was discovered, and, on the other hand, it was found that different cells of the same species differ absolutely in antigenic behavior. The blood-cells particularly differ from other organ cells, while there are also differences between the different organ cells of the same species. Experiments were made on the complicated subject of receptor relationships and receptor differences, with an attempt to differentiate and

characterize the numerous antigen functions of goat blood-cells as compared with other organ cells and blood-cells. Plant cells and organ cells of many animals (guinea-pigs, horses, cats, mice, dogs, turtles) share with goat blood the property of causing goat blood hemolysis in the rabbit. Therefore the organ cells of the aforesaid species must have receptors acting just like goat blood-corpuscles. The question remains whether the organ cells and the goat blood-corpuscles produce different or the same goat hemolysins and whether these different receptors are identical. For this purpose agglutinating experiments were performed, from which the following conclusions were drawn: (1) Goat blood possesses a receptor group which does not occur in the organ cells of guinea-pigs, mice, etc., *A* receptor. (2) Goat blood possesses a receptor group which is present in the aforesaid organ cells, *B* receptor. (3) Mouse erythrocytes do not have *B* receptors, but only a *C* receptor, also present in goat blood and the organs of guinea-pigs, mice, etc. (4) Goat blood has a *D* receptor which does not appear in the organ cells of the different species of animals nor in mouse blood, but which is present in the blood-corpuscles of cattle. (5) Hemolytic immune serums, which were obtained with the same antigen in different species of animals, seem to have varying degrees of avidity, that is the same amount of antigen combines from them different amounts of AE. (6) Hemolytic serums under otherwise equal conditions (for example the same titer) are more avid the less the receptor difference between the antigen and the serum donor.

The avidity of a hemolytic serum is dependent on the antigenic properties of the organ cells of the serum donor. If the body cells of the donor contain a large number of partial receptors which are also present in the red blood-cells used as antigen, a hemolytic serum of slight avidity is obtained. On the other hand, an animal body yields very avid hemolytic immune serums when it contains only a few partial receptor groups, or none at all, in common with the immunizing antigen.

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### **Amboceptors and Receptors. III. Intravital Fixing of Cell Antibodies.**

*J. Morgenroth and R. Bieling, Biochem. Ztschr., Berlin, 131: 541, Sept. 16, 1922.*

Irregularities found in testing the valency of mouse blood hemolysins in vitro led to similar tests in the animal body. If a rabbit that has been treated previously with bovine or dog's blood is injected again with the different erythrocytes, intravital hemolysis and hemoglobinuria take place. The serum of the mouse, in contrast with that of the rabbit and the guinea-pig, does not contain complete complement, but only intermediary bodies, while the end-body is lacking. Therefore it is not possible to activate an antigen-amboceptor mixture in vitro with mouse serum, even when mouse blood-corpuscles and inactivated mouse-blood-rabbit-serum are used for complement formation. Rosenthal called attention to the great divergence in the hemolytic action of mouse blood in vivo and in vitro and concludes from it that in vivo complements

must be present in mice and that possibly, in the process of bleeding, anticomplementary processes take place in the serum. It was shown in experiments that intravital hemolysis regularly takes place in the mouse if inactivated mouse hemolysin is injected into the animals.

From this it follows that the injection of inactivated serum of rabbits which have been previously treated with mouse blood-corpuscles causes intravital hemolysis in the mouse with hemoglobinuria and hemolytic icterus. This takes place even though the complement end-body is absent in the serum of the mouse. Fatal doses of mouse-tumor-rabbit-serum in carcinomatous mice are either delayed in action or do not act fatally at all. The injected cancer antibodies are deviated by the cancer cells of the body.

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**The Mechanism of Hemolysis and Agglutination by Ions.**

*F. Haffner, Pflüger's Arch. f. d. ges. Physiol., Berlin, 196: 15, Sept. 27, 1922.*

Agglutination, fixation and dissolution are common to all cell varieties and can be produced in vivo and in vitro by the most diverse agents. These phenomena must therefore depend on universal changes in the simplest structural elements common to the different varieties of cells. But the mechanism of such action is still obscure even in the case of simple chemical agents like H and OH or metallic ions. Hence, the modes of, and conditions pertaining to, the action of such ions and also of the anions of powerfully acting dye salts of the fluorescein group on red blood-corpuscles were investigated. Organic acids were also employed as anions, the cations as chlorids, the anions as sodium salts. The results were identical with beef, horse or mutton blood-corpuscles. The author subjected to minute analysis the action of anions in 0.9% sodium chlorid solution, the influence of the reaction, the mechanism of agglutination and fixation by ions and the influence of sodium chlorid on the same, the mechanism of hemolysis, the action of the ions on flocculation of the lysates by heat and alcohol and, finally, the mechanism of the internal action on hemoglobin. The results of this analysis are elucidated by abstracts from experimental data. The investigation yielded the following results. A series of electrolytes (acids, lyes and metallic and dye salts) show partly concordant, and for anions and cations characteristic and partly dissimilar effects on red blood-corpuscles. Agreement exists so far as moderate concentrations of electrolytes with active anion or active cation are lytic, while in stronger concentrations under definite conditions they act as fixatives and agglutinants. The action of anion is sharply differentiated from that of cation in that the fixative action of the former is promoted by increase of OH-ions, that of the latter by increase of H-ions. Some cations have an agglutinating action unattended by fixation, which takes place in low, partly sublytic concentrations. The nobler the metal the more preponderant the metallic ion's lytic action over its fixative action. With low cation concentration the agglutinating action without fixation depends on the flocculation of the stroma at and around its iso-electric point. Salts of trivalent metals act also in

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0.9% sodium chlorid solution, whereas stromas and corpuscles are precipitated by cations such as H and Hg only in an electrolyte-poor medium, as the stroma precipitation is arrested by neutral salt at its iso-electric point. Precipitation of the stroma depends on precipitation of the stroma substance in each individual cell which is manifested microscopically by stronger visibility of the cellular framework and by increased resistance of the cell toward lytic agents. The stroma substance behaves like a hydrophil colloid, its precipitation therefore depends on its dehydration and on production of the iso-electric reaction. On the other hand fixation and the associated agglutination by high ionic concentrations, as well as lysis which occurs with moderate ionic concentration, are conditioned exclusively by a change of state in the hemoglobin. Fixation is attended by precipitation, lysis by a reverse change of hemoglobin expressed by arrest or abolition of the hemoglobin precipitability by heat or alcohol. Lysis is to be regarded as the consequence of increased hydration of hemoglobin due to charging. This charging results from adsorptive or chemical addition of lytic ions. If the concentration of the oppositely charged ions in the reaction medium is sufficiently high the formation of a neutral, precipitating hemoglobin-cation-anion complex replaces the charging produced by co-addition of such ions. Charging of hemoglobin accelerates denaturation by heat and alcohol. It, too, leads to an irreversible change manifested by appearance of hematin and signs of dehydration (absence of neutralization), i.e. obviously splitting of the hemoglobin molecule. The hydrophobe product thus produced has the same precipitation sphere as the heat-denatured one; as a cation it has the color and spectrum characteristics of brown hematin, as an anion those of red hematin.

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**The Effect of Ions upon Agglutination.**

*Takuji Shionoya, Lancet, London, 203:905, Oct. 28, 1922.*

The true mechanism of agglutination is still unknown. The results obtained by Porges showed that agglutination is a physicochemic phenomenon in which the presence of salts is necessary, and that these cations play an important part in it. Experiments with cations of a valence greater than 3 had not hitherto been tried but it was evident that agglutination is closely related to the valence rule. This study aimed to investigate the effect of the valence of salts on the phenomenon of agglutination and to examine the effect of cations thereon. A pure salt-free agglutinin-bacteria combination was prepared by repeated washing of the agglutinin mixture with distilled water, followed by dialysis. Cobaltic complexes were used of valence 1-6 to test the effect of positive complex ions. It was found that as the valence of the cation increases, the limiting concentration with which agglutination takes place is decreased; also that a close relation exists between them as shown by plotting logarithmic curve of the limiting values and of the valences, with formation of a straight line. The precipitating action of the agglutinin-bacteria combination is entirely in accordance with the rule of valence and as precipitation occurs through the action of cations, it is a cation bearing negative electric charges. These findings are also

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applicable to hemagglutination, and the results of this line of investigation will be published later.

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**Agglutination of Washed Red Blood-Corpuscles by Colloidal Silica.**

*S. L. Cummins, Brit. J. Exper. Path., London, 3:260, Oct., 1922.*

The author observed that in opsonic mixtures containing diluted blood serum, there was immediate agglutination of the red corpuscles when washed blood suspension was added, although there seemed to be no such agglutination in preparations where the serum was more concentrated. As this seemed to point rather to an interference with the agglutination by strong serum than to an agglutinating action of the serum when diluted, it was necessary to ascertain whether the phenomenon could be reproduced with silica and salt solution in the absence of serum. Experiments demonstrated that colloidal silica solution, to which sufficient salt had been added to bring the mixture up to 0.75% of NaCl, brought about rapid agglutination of washed red blood-corpuscles which result could still be obtained after considerable dilution. So the agglutination was independent of the presence of serum. The apparent inhibition of the agglutination by the higher concentrations of serum is explained by the concomitant formation of a gel of sufficient firmness to hold mechanically the clumps from flocculating and sinking in the fluid, the inhibition disappearing as the serum is made more dilute.

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**On Heterogenetic Agglutinins.**

*Trou-Hia-Hsü, Ztschr. f. Immunitätsf. u. exper. Ther., Jena, 34: 507, Sept. 30, 1922.*

High titer sheep blood hemolysins can be produced in rabbits by the preliminary injection of organ emulsions of the guinea-pig, as well as a series of other animal species. Like the specific isogenetic hemolysins, these hemolysins, designated as heterogenetic, by Friedberger and Schiff, possess the characteristic properties of amboceptors. The isogenetic amboceptors can be distinguished from the heterogenetic only by the greater specificity of the latter. In investigating whether differences similar to those existing among bacterial agglutinins, could be found in the isogenetic and heterogenetic sheep blood anti-serums, it appeared that under ordinary conditions a hemagglutinin for sheep blood cannot be demonstrated in heterogenetic sheep blood antisera; this was shown in corroborating earlier tests by Forssmann, as well as by Friedberger and Schiff. The rapidity of sedimentation of blood-corpuscles is not increased by the addition of heterogenetic serum, in contrast to the effect of adding isogenetic serum. Nevertheless, specific agglutinins for sheep blood-cells are present in the heterogenetic anti-serum, but they can be demonstrated only in blood several days old.

Heterogenetic agglutinin is specific for serum and antigen, i.e. neither does another amboceptor act upon old sheep blood, nor does the

heterogenetic sheep serum act with other species of blood-corpuscles, e.g. old beef blood. No difference could be found in the shape of the floccules when sheep blood was agglutinated by isogenetic or by heterogenetic sheep antiserums. The agglutinating power appears only when the blood has been kept in the incubator for 2 days, or at room temperature for 3 days. The bacteria in the suspension appear to have no influence upon the production of agglutination. Fresh blood-corpuscles suspended in the decanted fluid from an old suspension, are not agglutinated. The author did not succeed in the attempt to sensitize sheep blood-corpuscles for the heterogenetic antigen by means of heat, alcohol, ether or osmic acid, instead of storing. The effect of higher temperatures is the same upon isogenetic as upon heterogenetic agglutinins.

The absorption tests gave the following results: The isogenetic agglutinin is completely absorbed by fresh and aged sheep blood-corpuscles, partly absorbed by corpuscles heated to 100° C., and not at all absorbed by beef blood-corpuscles and guinea-pig renal cells. The heterogenetic agglutinin is absorbed by the same substratums, and in addition by guinea-pig kidney cells. Hence there are 2 agglutinins, those which show an affinity for guinea-pig kidney, and those which have no demonstrable relation to that organ. Fresh sheep blood-corpuscles, as well as those several days old, possess at least 2 groups of receptors, one of which is taken up by the agglutinin of the isoserum, the other by that of the heteroserum. Heating to 100° markedly weakens the isoreceptor, while the heteroreceptor is thermostabile. Beef blood-corpuscles are neither agglutinated nor fixed by either isoserum or heteroserum, i.e. they lack both the isoreceptors and the heteroreceptors of agglutination. These differences indicate that the structure of the thermostabile portion of the receptor apparatus is more complicated than has hitherto been assumed on the basis of hemolytic tests.

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**Studies in Group Agglutination. I. The Salmonella Group and Its Antigenic Structure.**

*F. W. Andrewes, J. Path. & Bacteriol., Edinburgh, 25: 505, Oct., 1922.*

The phenomenon of group agglutination is seen in its most highly developed form among the Salmonellas. The author's observations herein recorded were limited to 4 organisms—*Bacillus paratyphosus* B and C, *B. aertrycke* and the Newport bacillus—and to the peculiarly intimate form of group agglutination which subsists among them. The problem to be solved lay in the determination of the proportions and distribution of the assumed specific and group properties in the types of *Salmonella* studied; in other words, it was desired to effect an analysis of the antigens in the bacteria, and of the agglutinins in their respective serums. It was necessary to find for bacterial analysis serums containing pure group agglutinin and pure specific agglutinin respectively. Similarly, for serum analysis bacterial strains were needed containing one or the other antigen in a relatively pure state. Pure specific serums were readily obtained for each type by exhausting ordinary serums of all their group agglutinin. For pure group serums any allied serum

may be used, provided that it is known to be rich in group agglutinin. The author's experimental evidence indicates that in all mass cultures there exist, side by side, 2 types of bacilli, and only 2, sharply differentiated in their antigenic structure. The one contains the specific antigen and the other the group antigen but neither is absolutely pure. The specific bacillus contains traces of group antigen and vice versa.

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**The Racial Distribution of Isohemagglutinin Groups.**

*Julian H. Lewis and Deborah L. Henderson, J. A. M. A., 79: 1422, Oct. 21, 1922.*

There exist in the blood 2 types of specific agglutinating substances, *a* and *b*. In the red cells are 2 specific types of agglutininogenic substances, *A* and *B*. Obviously, one type of agglutinin will occur only in the absence of its corresponding agglutininogen. This distribution of agglutinins and agglutininogens makes it possible to divide all samples of human blood into 4 different groups (Jansky) containing: (1) both types of specific agglutinin; (2) agglutinin *b* and agglutininogen *A*; (3) agglutinin *a* and agglutininogen *B*; (4) both agglutininogens.

According to H. and L. Hirschfeld, who examined about 8000 samples of blood from the various races assembled in Europe during the recent war, the distribution of the 4 groups of hemagglutinins among these people varied extremely, but certain races could be grouped together because of the similarity in the distribution among them of the specific agglutinins *a* and *b*. This grouping of races corresponded somewhat to the grouping made on an anthropologic basis; it corresponded still more completely to the geographic distribution of the races. It was found that the European type, including Englishmen, Frenchmen; Italians, Germans, Austrians, Bulgarians, Serbians and Greeks, is characterized by the prevalence of Group II of the hemagglutinins and a low incidence of Group III. Among the Asio-African group, including Malagasies, Negroes, Anameses and Hindus, the incidence of Group II is low, while that of Group III is high. There is an intermediate type including Turks, Arabs, Russians and Jews, in which the 2 groups occur intermediate to that of the European and Asio-African types. The proportion of the prevalence of agglutinin *a* and agglutinin *b* in each race is expressed numerically as a biochemic race index. The race index for the European peoples varies between 4.5 and 2.5; for the Asio-African peoples it is 1 or less, while the intermediate type is characterized by a race index of 1-2. Since the difference in the distribution of hemagglutinin groups among African and American Negroes lies in the direction of an approach to the distribution among the white race, it is assumed that the change is due to intermixture with the latter.

This is an important contribution to anthropologic methods because it is a characteristic with a biochemic basis and is therefore definite and susceptible of accurate study. Some of the uses that the method may serve are pointed out by the Hirschfelds. They seem to find evidence in their work that suggests 2 sources of origin of the

human race, one in India, where agglutinin *a* arose, and the other in western or central Europe, where agglutinin *b* had its origin. It is believed that further examination of the northern races will lead to definite conclusions as to this view. The relations of races as indicated by the hemagglutinins are in some instances inconsistent with those previously established by the usual methods of anthropology.

A given kind of specific agglutinin or agglutininogen never occurs in a child unless it is present in one of the parents, and when one of these substances is present in both parents it occurs in most of the children. When one of the substances occurs in only one parent, some of the children inherit it, and when neither parent has one of the substances no child ever shows it. This fact would seem to indicate that the findings of the Hirschfelds are not accidental but are true racial characteristics, the perpetuity of which is insured.

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### **The Hemagglutinating Fraction of Human Serums.**

*Rufus L. Holt and Francois H. K. Reynolds, J. A. M. A., 79: 1684, Nov. 11, 1922.*

In the authors' experiments the serums of Groups II and III were obtained and fractioned according to Banzhaf's method, except that the serum was used instead of the citrated plasma. Ten cubic centimeters of serum were diluted with 5 c.c. distilled water, and to this was added 6.43 c.c. saturated ammonium sulphate solution. This gave a 30% saturation with saturated ammonium sulphate solution, and precipitated the euglobulin. The 2 specimens were centrifuged at high speed, throwing down the euglobulin and allowing the supernatant fluid to be pipetted off. The supernatant fluid was then raised to 50% saturation by the addition of 4 c.c. of the saturated ammonium sulphate solution, precipitating the pseudoglobulin, which was separated by the same method as that used for the euglobulin. The remaining supernatant fluid contained albumin. The 2 samples of euglobulin, the 2 samples of pseudoglobulin and the remaining supernatant fluids containing albumin from the 2 groups were placed in separate Schleicher and Schull thimbles and dialyzed for 48 hours in running tap water to remove the sulphate. They were then transferred to distilled water for 24 hours, since the tap water contained natural sulphates. They were again transferred to fresh distilled water, and this water was found free of sulphates after immersion of the dialyzing thimbles for 24 hours. The 3 fractions from the serum of the 2 groups (II and III) were then tested against the cells of Groups I, II, III and IV, the Moss classification being employed. The albumins were used as they came from the dialyzing thimbles. Parts of the euglobulin and pseudoglobulin from each of the 2 samples were dissolved in a small amount of physiologic sodium chlorid solution. Groups I, II, III and IV cells were suspended in physiologic sodium chlorid solution, and groupings were set up on glass slides. They were checked both microscopically and macroscopically. The tabulated results show that the hemagglutinating property is contained in the pseudoglobulin fraction, the euglobulin and albumin apparently playing no part in the reaction.

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**An Automatic Distributing Apparatus.**

*Leon H. Cornwall and George Philipp Schmitt, J. Lab. & Clin. Med., 8: 56, Oct., 1922.*

The function of this apparatus is to distribute rapidly a measured amount of any required liquid ingredient to a large number of test-tubes or other containers. The apparatus consists of 2 separate sections, one of glass through which the measured liquid is aspirated and delivered, and the other of metal for the automatic operation of the first. The glass section consists of tubing of the approximate size and caliber of the ordinary 1 c.c. pipets. There is a vertical and a curved horizontal portion, in both of which there are bulbous dilatations, each containing a conical glass bead. The lower ends of these bulbous dilatations are conical and ground so that the beads fit tightly into them. By this arrangement the beads act as opposing valves. When one valve is open the other is closed and vice versa. This allows fluid to be aspirated into a syringe that is connected to the upper end of the vertical arm and delivered through the curved horizontal arm. The syringe may be fitted into a ground aperture prepared for it and removed when desired or it may be a continuation of the vertical tubing.

The operating mechanism, of metal, is designed on the principle of a vertically disposed syringe. The piston, instead of being operated by traction, is elevated by air forced into the barrel by a bulb that is manipulated by the operator. The piston descends by gravity when the pressure on the bulb is released. On one side of the metal piston there is a lug which projects through a longitudinal slit in the barrel. The outside of the barrel is threaded and has a nut which may be screwed up or down. The excursion of the piston is regulated by adjustment of the movable nut against which the lug on the piston impinges when air is forced in. An arm projects from the upper end of the metal piston and engages the upper end of the glass piston. The whole apparatus may be attached to a ring stand or clamped to the neck of a bottle or flask. When maintenance of sterility is essential the glass parts may be sterilized by boiling and the vertical tube can be inserted through the stopper of a bottle or flask. Contamination may be avoided by flaming the glass tip before use and then sealing it by some simple device, such as hot paraffin.

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**Studies of Gas and Electrolyte Equilibria in the Blood. III. The Alkali-Binding and Buffer Values of Oxyhemoglobin and Reduced Hemoglobin.**

*Donald D. Van Slyke, A. Baird Hastings, Michael Heidelberger and James M. Neill, J. Biol. Chem., 54: 481, Oct., 1922.*

The general problem, a portion of which the present paper attempts to solve, has been outlined in the first of these studies. The object of the present work was to determine quantitatively, on solutions of hemoglobin free from other proteins, the following data: (1) the amounts of base bound by oxyhemoglobin and reduced hemoglobin,

respectively, at normal blood pH; (2) the changes in the base bound by oxyhemoglobin and reduced hemoglobin with changing pH; (3) the nature of the curve relating oxygen increase to the increase in base bound at constant pH that occurs as reduced hemoglobin adds varying amounts of oxygen. In the authors' experiments the hemoglobin was dissolved to make about the same concentration found in horse blood, about 7 mm. (equivalent to 15-16 volumes per cent. of oxygen capacity), and the amount of alkali added was such that the system at physiologically normal carbon dioxide tensions had pH values within physiologic limits. The saturations were performed at 38° with the double tonometer previously described by the authors. It was found that the alkali (Na) bound at pH 7.4 per gram molecule of recrystallized horse oxyhemoglobin is  $2.15 \pm 0.10$  equivalents, while that per gram molecule of reduced hemoglobin was found to be  $1.47 \pm 0.08$ . In these calculations a gram molecule of hemoglobin has been taken as the amount combining with a gram molecule of oxygen. At pH 7.4, the change of 1 mol of reduced hemoglobin to oxyhemoglobin enables the hemoglobin to combine with  $0.68 \pm 0.10$  equivalent of additional alkali. For points intermediate between complete oxygenation and complete reduction, increase in base bound at constant pH is in simple direct proportion to increase in oxygen content.

(The greater portion of this article is given over to the presentation of graphic, tabulated and mathematical data.)

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**Studies of Gas and Electrolyte Equilibria in the Blood.  
IV. The Effect of Oxygenation and Reduction on the Bicarbonate  
Content and Buffer Value of Blood.**

*Donald D. Van Slyke, A. Baird Hastings and James M. Neill,  
J. Biol. Chem., 54: 507, Oct., 1922.*

Among other things, the authors wished to determine in these experiments (1) the buffer value of oxygenated and reduced blood, and the proportion of it for which hemoglobin is responsible; also (2) the quantitative effect of change in combined oxygen at constant pH on the blood bicarbonate. The same experimental methods were employed as in the preceding article. The blood, drawn from a horse the night before each experiment, was saturated at 38° under known tensions of CO<sub>2</sub> and O<sub>2</sub>, and the changes in base distribution were estimated from changes in the bicarbonate. The buffer values of each of 3 samples of oxygenated blood from the same horse, the degree of oxygenation being constant, were found to be constant over the pH range 7.2 to 7.5. In the oxygenated blood the hemoglobin was calculated to be responsible for an average of 76% of the total buffer value, bicarbonate for 6.9%. In reduced hemoglobin the figures were 73.3 and 9, respectively. From the effect of oxygenation and reduction on the buffer value of blood, it is estimated that if the molecular buffer value of oxyhemoglobin is 2.64, as found in the preceding paper, the molecular buffer value of reduced hemoglobin is 2.45.

(The greater portion of this article is given over to the presentation of graphic, tabulated and mathematical data.)

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**Investigations on the Oxygen Content of Cutaneous Blood (So-Called Capillary Blood).**

*Christen Lundsgaard and Eggert Möller, J. Exper. Med., 36: 559, Nov. 1, 1922.*

In these experiments the authors have studied the composition of the cutaneous blood and especially its relation to arterial blood. They have used the oxygen content as an indicator of the nature of the blood, because the amount of oxygen in the blood usually changes during the blood flow through the capillaries, and because oxygen, unlike all other substances in the blood, has the property that its maximum amount in the blood can be determined outside the body, this being equal to the sum of the total oxygen capacity of the hemoglobin and the amount dissolved in the plasma.

Arterial puncture was performed according to the technic of Hürter, Stadie, and Harrop, while venous puncture was done according to Lundsgaard's procedure. Cutaneous blood was collected under oil in a jar from the incised finger tip. As a rule, 3-4 c.c. blood could be obtained from the finger in 1-2 minutes. Van Slyke's method was employed for determining the oxygen content of the blood. The total oxygen capacity was estimated either by a standardized Autenrieth colorimeter, or by saturating a sample of blood and determining the amount of oxygen.

The results indicate that the oxygen content of cutaneous blood and of arterial blood may show almost identical values. This was true not only of normal individuals before and after exercise, but was also found to hold under different pathologic conditions. This is sufficient to show that, in some instances, one might obtain similar information from samples of cutaneous and of arterial blood. The authors think they are justified in extending the identity existing between the oxygen content of the arterial and cutaneous blood to other substances in the blood, for instance sugar, salt, uric acid, etc., and also to the reaction of the blood. They are unable to say whether this identity is always true; for example, in a patient with increased venous pressure. Furthermore, it was shown that unless the perfusion of the skin has been extremely great during the experiment, samples of blood obtained from a skin incision (of the finger) cannot represent the true capillary blood. The neutral expression "cutaneous blood" seems, therefore, for the present preferable to the term "capillary blood" for samples of blood obtained by cutaneous incisions.

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**The Determination of Blood Catalase, with Observations on the Factors Affecting the Ratio between Quantity and Activity of This Enzyme.**

*Ruth Okey, Am. J. Physiol., 62: 417, Nov. 1, 1922.*

This work was undertaken to ascertain whether or not an adaptation of Van Thienen's "Katalase Index" determination might be of  
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value as a clinical method for distinguishing primary from secondary anemias. The use of a catalase determination as a diagnostic aid implies, however, a preliminary study of the reaction involved and the factors bringing about differences in the results obtained.

The factors affecting the ratio between the amount and activity of the enzyme are: (1) Hydrogen-ion concentrations. Acid or alkali in any considerable amount destroys the enzyme, so in the determinations reported by the author the hydrogen-ion concentration of the peroxid was adjusted to approximately pH 7.5 by neutralization with 0.1 n. NaOH with the aid of outside indicators. (2) Temperature. The enzyme is increasingly destroyed as the temperature at which the reaction is allowed to proceed is set at a higher level. (3) Concentration of enzyme. Generally speaking, the lower the concentration of the enzyme the shorter the time necessary to reach the equilibrium point. (4) Relative quantity and concentration of substrate. The author found that within certain limits, i.e. when the amount of peroxid decomposed is about 25-60% of the total, and the amount and concentration of hydrogen peroxid is kept constant throughout a series of measurements, the amount of peroxid decomposed at the equilibrium point may be relied upon to be directly proportional to the amount of enzyme acting, provided, of course, other reasons for variation are eliminated. Too great relative variation in the concentration of enzyme or substrate will lead to a departure from this relationship. (5) The state of suspension of the enzyme: (a) Laking the blood. It has been repeatedly shown that the catalase of water dilutions of blood is not destroyed any more rapidly by standing after dilution than that of suspensions of corpuscles in normal saline; therefore, it would seem that the change which takes place when the blood is laked represents rather an alteration in the state of dispersion of the enzyme than an actual destruction of the catalase. (b) Heating the enzyme dilutions. The activation of the enzyme reported by Euler and his coworkers to be produced by heating saline suspensions of blood corpuscles to 55-57° C. seems to be a transient effect apparent only during the first 10 minutes of the reaction, and possibly due to the laking of the corpuscles. (6) Antiseptics. Xylene and toluene are the best preservatives for blood dilutions to be used for catalase determinations. Chloroform and formaldehyd should be avoided.

In the author's procedure the enzyme solutions were distilled water dilutions of whole (human) blood. One cubic centimer of whole blood or corpuscles was measured with an Ostwald pipet into a 100 c.c. volumetric flask partially filled with distilled water or 0.89% sodium chlorid solution. The flask was filled to the mark with the diluting fluid, the contents mixed, and further dilutions made in the same way, whole blood being diluted in the proportion of 1 part blood to 999 diluent for the standard catalase determination. For the determination of the standard blood catalase value, 1 c.c. of neutralized hydrogen peroxid solution (3%) was measured with an Ostwald pipet into a clean, dry pyrex Erlenmeyer flask of about 100 c.c. capacity. This was diluted with 9 c.c. distilled water. Then 1 c.c. of the enzyme solution was measured into the flask with an Ostwald pipet, and the time at which the enzyme was added carefully noted. The contents of the flask were then mixed by a rotary movement and the flask with its contents allowed to stand untouched for the desired length of time.

When this had passed, the reaction was brought to an end by the addition of 10 c.c. of 10% sulphuric acid, and the contents of the flask titrated with a standard potassium permanganate solution of such a strength that 1 c.c. of the solution was equal to 2 mg. of hydrogen peroxid. Control determinations were made in which 1 c.c. of the hydrogen peroxid was diluted with water in the same way, 1 c.c. of the boiled catalase solution was added, the contents of the flask allowed to stand for the same lengths of time, treated with acid, and finally titrated as described above. The figure for hydrogen peroxid decomposed was thus determined by difference.

The author will not commit herself, at present, as to the extent to which the determination of catalase activity may have clinical or physiologic significance.

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**The Effect of Warm and Cold Weather on the Blood Catalase.**

*W. E. Burge and J. M. Leichsenring, J. Lab. & Clin. Med., 8:33, Oct., 1922.*

This investigation attempts to determine the mode of action of cold in increasing oxidation in the body. For several years the authors have conducted experiments in which oxidation in animals was both increased and decreased in practically every known way. Invariably it was found that whenever oxidation is increased, catalase, an enzyme possessing the property of liberating oxygen from hydrogen peroxid, was also increased and whenever oxidation was decreased, catalase was decreased. Hence they naturally turned to this enzyme in their attempt to find an explanation for the increased oxidation brought about by cold weather. The animals used were rabbits. Catalase determinations were made by adding 1 c.c. blood diluted 1-3 with 0.9% sodium chlorid to 200 c.c. neutral hydrogen peroxid and the amount of oxygen liberated in 10 minutes was taken as a measure of the catalase content of the blood.

A comparison was made of the catalase content of the blood of rabbits in summer and in winter. It was found that the blood catalase in summer, when the average temperature was 74° F., was much lower than that of rabbits in winter, when the average temperature was 30° F. The average amount of oxygen liberated by 1 c.c. diluted rabbits' blood in summer was 825 c.c., while it was 1200 c.c. in winter. Catalase determinations were made of the blood of rabbits for each month from August to April inclusive. The temperature fell from 73° F. in August to 25° F. in the following January, and there was an increase in catalase during this period, indicated by the fact that in August 1 c.c. diluted blood liberated 800 c.c. oxygen from hydrogen peroxid in 10 minutes, whereas in January 1 c.c. diluted blood liberated 1120 c.c. in a like period.

Comparison was made of the blood catalase of Illinois and Louisiana rabbits in December. The temperature in Illinois was 33° F., while in Louisiana it was 70° F. The average amount of oxygen liberated by the blood of the 5 Illinois rabbits was 1014 c.c., while



the blood of the Louisiana rabbits liberated only 769 c.c. The blood of rabbits brought from Louisiana, where it was warm, to Illinois, where it was cold, showed a considerable increase in catalase. The increase in oxidation in warm-blooded animals brought about by cold weather is attributed to an increase in catalase and the decrease in oxidation brought about by warm weather is believed to be due to a decrease in catalase.

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### **A Rapid Method of Blood Analysis.**

*Richard Weiss, New York M. J., 116:585, Nov. 15, 1922.*

*Quantitative Determination of Sugar.*—This method was given in detail in the SURVEY, Jan., 1922, 1e-109.

*Quantitative Determination of Calcium.*—According to the method of de Waard, blood serum is placed in the container up to the mark S, and a saturated solution of ammonium oxalate is added up to the mark AO. After shaking, the mixture is allowed to stand for  $\frac{1}{2}$  hr., when the glass is centrifuged rapidly for 3-5 minutes. The fluid above the precipitate is removed carefully, the precipitate is washed 3 times by adding about 2 c.c. distilled water, mixing, centrifuging and removing the supernatant solution. Sulphuric acid is then added up to the mark SS and warm water (about 60° C.) poured in up to the mark O. Titration is performed by running in drops of 0.01 n. solution of potassium permanganate. The glass is shaken constantly and dipped into a water-bath at 60° C. from time to time. When a red color appears that lasts for 2 minutes, the titration is completed.

*Determination of Bilirubin.*—Meulengracht employs the yellowish color of the bilirubin itself as an indicator and determines its quantity by the simple process of dilution. About 3 c.c. blood is taken from a vein of the arm and placed in a small Wassermann tube, containing 2-3 drops of 20% sodium citrate solution to prevent coagulation. The tube is allowed to stand for a few hours when the blood-corpuscles will have settled to the bottom. The supernatant serum is then poured into the bilirubinometer up to the mark S. This vessel has the same caliber as another tube which contains the faintly yellow standard solution. Saline (0.9%) solution is then added to the serum until it shows the same hue as the standard. The reading is best done by direct illumination against a white background. For calculations, the concentration of the standard is termed 1 (corresponding approximately to the color of normal serum). To obtain this color in normal cases it may be necessary to dilute the serum 2-3 times, while in pronounced icterus the dilutions may vary from 100-200.

*Flocculation Reaction for Syphilis.*—Weiss claims that the Sachs-Georgi, Meinicke and Dold reactions can almost substitute the original Wassermann reaction as they coincide with it in 90% of cases. In serums known to be syphilitic, a definite flocculation occurs when a cholerestitized extract of human or beef heart, with saline solution, is added. This may best be determined if the tube is viewed against a black plate, turned and inspected through a magnifying lens.

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**Extraction of Histidin from Blood.**

*S. Demjanowski, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122: 93, Sept. 16, 1922.*

The parent material was defibrinated ox or horse blood, either in the liquid state or coagulated by heat and freed from serum by expression. Hydrolysis was carried out in a small autoclave under increased, or in flasks under ordinary pressure. The requisite acids for hydrolysis, their concentration, and duration of hydrolysis varied. Sulphuric and hydrochloric acid were employed. With the latter hydrolysis was more rapid and more complete. When the autoclave was employed hydrolysis was applicable to large quantities of blood. Further treatment was carried out by Kossel's method which has been modified by Pauli, Knoop and S. Fraenkel. About 90 gm. crude histidin chlorid was obtained from 8333 c.c. blood.

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**A Gasometric Method for the Determination of Urea Nitrogen in the Blood.**

*A. Mirkin, J. Lab. & Clin. Med., 8: 50, Oct., 1922.*

The technic described is as follows: (A) Test for total CO<sub>2</sub>, 2 c.c. plasma, 1 c.c. urease. (B) Test for preformed CO<sub>2</sub>, 2 c.c. plasma, 1 c.c. H<sub>2</sub>O (free from CO<sub>2</sub>). Incubate A and B for about 10 minutes at 45-50° C. Cool with running water to room temperature. Run exactly 1.5 c.c. of A into Van Slyke's apparatus, add 0.5 c.c. distilled water free from CO<sub>2</sub> and determine CO<sub>2</sub> in the usual way. Do the same with B. For calculation, this formula is used:  $Ur_{100} = 63.6 \frac{V_1 - V_2}{Wpt.}$   $Ur_{100}$  = the amount of urea nitrogen per 100 c.c. blood;  $V_1$  = Volume of CO<sub>2</sub> yielded by A;  $V_2$  = Volume of CO<sub>2</sub> yielded by B; Wpt = Weight of 1 c.c. CO<sub>2</sub> at the temperature and pressure prevailing during the test.

$$63.6 = \frac{NH_2 \cdot CO \cdot NH_2}{CO_2} \times \frac{N_2}{NH_2 \cdot CO \cdot NH_2} \times 100 = \frac{2800}{44} = 63.6$$

Care in carrying out the procedure is of the utmost importance. The apparatus must be absolutely airtight, the stop-cocks well greased, and all precautions recommended when carrying out gasometric determinations must be painstakingly observed. Not more than 0.01 c.c. caprylic alcohol should be added to prevent foaming, as an excess makes exact reading more difficult. This gasometric method gives accurate results as compared with the colorimetric methods.

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**A System of Blood Analysis. IV. A Revision of the Method for Determining Uric Acid.**

*Otto Folin, J. Biol. Chem., 54: 153, Oct., 1922.*

After further experimentation the author says he is no longer able to repeat his previous statement that 95-100% of uric acid is recoverable in the tungstic acid blood filtrate prepared according to the directions of Folin and Wu. Such high figures were doubtless due to the fact that the investigators were dealing with samples of blood that

did not possess any great tendency to retain uric acid. Folin has investigated the extent to which uric acid added to sheep blood goes into the filtrate, employing the direct determination method and eliminating all possibility of error due to unknown constituents by adding to the standard uric acid solution the same quantity of the sheep blood filtrate as was used for the determination. The filtrate added to the standard was prepared from the same blood, but contained no uric acid. The necessary solutions are: (1) Diluted uric acid standard containing 0.02 mg. uric acid in 5 c.c. From the standard uric acid formaldehyd solution, containing 1 mg. per c.c., transfer 1 c.c. to a 250 c.c. volumetric flask. Half fill the flask with water and add 10 c.c. of the 0.66 n. sulphuric acid used in the blood protein precipitation. Add also 1 c.c. 40% formaldehyd and then dilute to volume, mix, and date. (2) Uric acid reagent of Folin and Denis. (3) Lithium sulphate solution, prepared by dissolving 20 gm. powdered lithium sulphate in about 80 c.c. cold water. Dilute to a volume of 100 c.c. and filter. (4) Approximately 15% solution of sodium cyanid in 0.1 n. sodium hydroxid. Blank tests to determine the presence or absence of reducing substances in the cyanid solution must be made as a precaution.

For the uric acid determination half fill a wide liter beaker with water and heat to boiling. Transfer 5 c.c. blood filtrate and 2 c.c. water to one test-tube graduated at the 25 c.c. mark, and transfer 5 c.c. standard uric acid solution and 2 c.c. water to another similar test-tube. Add 2 or 3 drops of 20% lithium sulphate solution to each. From a buret add 2 c.c. 15% sodium cyanid solution. By means of a graduated pipet add 1 c.c. uric acid reagent of Folin and Denis to each test-tube. Mix, and let stand for 2 minutes, when both tubes should be transferred to boiling water and allowed to remain 80 seconds. Cool, dilute to volume, and make the color comparison in the usual manner, not omitting first to read the standard against itself. When the standard is set at 20 mm., 20 divided by the reading of the unknown, times 4, gives the uric acid content in milligrams per 100 c.c. blood. The proportionality of the color obtained is so good that, if the cyanid is right, readings between 10 and 40 mm., covering a range of 2 to 8 mg., are dependable.

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#### The Determination of Uric Acid.

*Stanley R. Benedict, J. Biol. Chem., 54:223, Oct., 1922.*

The report of Folin that the blood of one species (sheep) behaves differently at different times in regard to uric acid recovery merely emphasizes the fact, in Benedict's opinion, that uric acid determination is a different problem for the blood of each species. Benedict also believes it unwise to adopt the exceedingly slow process of protein precipitation suggested by Folin. The latter's implied criticism of Benedict for employing a new reagent (arsenic phosphotungstic acid) is answered with the statement that abandonment of the Folin-Denis reagent became necessary because of the turbidity produced and the lack of proportionality of color when very little uric acid was used. The new reagent has less tendency to turbidity and is prepared with 20 minutes' boiling as against several hours for the old reagent. Folin has recommended as one of the reagents in the determination of uric acid a 15%

sodium cyanid solution that is at least two weeks old, while Benedict finds a 5% solution (to which has been added a trace of ammonia) entirely adequate. The addition of sodium hydroxid to this solution is unnecessary. In a uric acid solution which Benedict has been studying, oxidation of uric acid is prevented by lowering the dissociation by means of hydrochloric acid, and by lowering the oxygen tension of the solution. Procedure: About 8 liters of the dilute standard solution required for the uric acid determination in blood, and containing hydrochloric acid, are prepared by the method described by the author in a previous article, and placed in a narrow-mouthed bottle of about 10 liters' capacity. This bottle is fitted with a new, 2 holed rubber stopper. Through one hole passes a long glass tube, reaching nearly to the bottom of the bottle, and which after passing out through the stopper is bent sharply so that its lower end reaches somewhat below the bottom of the bottle on the outside. The end of this tube is fitted with a short piece of clean rubber tubing and a spring clamp. Through the other hole in the stopper passes a second glass tube, terminating an inch or more above the surface of the liquid in the bottle. This tube is preferably bent at right angles where it emerges through the stopper, and is also fitted with a short rubber tube and a spring clamp. A Kipp generator, charged with broken marble and hydrochloric acid, and fitted with a wash bottle, is now connected with the long tube which reaches nearly to the bottom of the standard solution. Both spring clamps on the tubes to the bottle are opened and a moderately brisk stream of carbon dioxid is passed through the solution for about 30 minutes. While the generator is still turned on, the outlet tube from the bottle is first closed with the spring clamp, so that carbon dioxid collects in the bottle under pressure. Then the inlet tube is similarly closed and the generator turned off and disconnected. The bottle of standard solution is placed upon a convenient shelf, together with the Kipp generator which is now connected with the short tube which terminates above the solution, and the generator stop-cock opened wide. The spring clamp which closed this tube is also opened, and left open. Standard solution can now be withdrawn as needed by opening the spring clamp on the lower tube, and the volume leaving the bottle is immediately replaced by carbon dioxid from the generator. As the whole system is under pressure of carbon dioxid there is no tendency for air (oxygen) to enter it at any time. The first few cubic centimeters of solution withdrawn are best discarded, and the rest kept in a glass-stoppered bottle. This solution can be absolutely relied upon for 2 weeks after taking it from the large bottle.

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**The Distribution of Sugar, Residual Nitrogen and Calcium in the Blood.**

*I. K. Parnas and W. von Jasinski, Klin. Wchnschr., Berlin, 1:2029, Oct. 7, 1922.*

Blood was collected from the arm veins of young, athletic men 20-30 years old, through a large platinum needle covered with paraffin, into paraffined, graduated centrifuge tubes, covered with vaselin which liquefied at 40° C., and was centrifuged. After 2 minutes plasma was removed with paraffined pipets, made uncoagulable with oxalate, and the

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rest centrifuged again. Then a specimen was taken from the middle of the blood-corpuscle column. With this method the blood-corpuscles suffer very little from the coagulation process. In normal young men in whom the blood sugar content was 0.97-1.125%, the sugar content of the pure plasma was identical with that of the oxalated or citrated plasma; the erythrocytes centrifuged to 50% of the volume contained 85-100% of the amount of sugar which the plasma contained. Between the determinations of glucose in the genuine plasma and the total blood there were only slight differences. After dealbuminization by the method of Folin and Wu, the residual nitrogen in the genuine plasma and in the oxalated or citrated plasma was identical. In the blood-corpuscles, the author found the same amount of, or a little less, residual nitrogen as in the plasma or total blood. The blood-corpuscles were not free of calcium. The analysis of the centrifuged, unwashed corpuscles showed that the erythrocytes had 7.5-8% of the calcium content that the plasma had.

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**A Micromethod for Determining Ethyl Alcohol in the Blood.**

*Erik M. P. Widmark, Biochem. Ztschr., Berlin, 131:473, Sept. 16, 1922.*

To determine indirectly the changes of alcohol content in the blood by determining those in the urine certainly has an advantage but there is not an equilibrium of diffusion between alcohol and blood under all experimental conditions. Therefore an attempt was made to find a micromethod for determining the ethyl alcohol content of the blood, for which purpose the amount of blood obtained by puncture of the fingertip (about 100 mg.) was sufficient. The bichromate method was used. An apparatus suitable for it was devised by Grave in Stockholm. Blood was drawn into this apparatus by means of a capillary pipet, weighed on a torsion scale, and blown out. Definite amounts of bichromate-sulphuric acid solution were put into 2 other flasks and all dried on a water bath at 50° and 60° C. Then 25 c.c. distilled water was added to each flask, carefully shaken and 0.5 c.c. potassium iodid added and afterward titrated with a 0.005 n. thiosulphate solution. The difference between the consumption of thiosulphate in the test solution and the blood is proportional to the amount of alcohol in the blood. The following formula is used for the calculation:  $x = 1.13 (b-a)$ , in which  $x$  is the unknown amount of alcohol in  $y$ ,  $b$  the consumption in the test solution and  $a$  that in the blood solution of a 0.01 n. thiosulphate solution expressed in hundredths of a cubic centimeter. If a 0.005 n. thiosulphate solution is used, the comparative factor is half as large, that is 0.57. As to the sensitiveness of the test, after taking 5 gm. alcohol it can be definitely demonstrated in the blood.

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**Evaluation of Buffers of the Blood.**

*Edward A. Doisy, A. P. Briggs, Emily P. Eaton and William H. Chambers, J. Biol. Chem., 54:305, Oct., 1922.*

The authors collected the data necessary for a recalculation of the degree of participation of the various buffers in the transport of carbon



dioxid. This work involved a study of the effect of oxygen unsaturation, determinations of the carbon dioxid dissociation curves of oxygenated and reduced blood, of separated sera and of dialyzed hemoglobin to which bicarbonate had been added, and inorganic phosphate analyses of the blood and serum. The buffer systems studied were identical with those discussed by Van Slyke. The carbon dioxid and oxygen analyses were made by the technic described by Van Slyke and Stadie, and the phosphate analyses by the method of Bell and Doisy as modified by Briggs. The gas mixtures were analyzed with a Henderson buret. The data obtained included the carbon dioxid absorption curves of oxygenated blood or reduced blood, of separated serum, of a hemoglobin-bicarbonate solution, and of phosphate analyses of blood and serum upon a single sample of blood (in the case of one of the subjects) and upon 2 different samples of blood of another subject. In addition, the authors determined the  $O_2$  and  $CO_2$  content of one or more samples of venous blood from each of these subjects. From the detailed tabulated and graphic data presented in the article one learns that in the authors' study of the various known buffer systems of the blood they have been able to account for 87-97% of the carbon dioxid carried in the change from an hypothetical arterial to an actual venous state.

As previously pointed out by Van Slyke (1921), the hemoglobin plays the preëminent rôle in the transport of both carbon dioxid and oxygen. About 75-80% of the carbon dioxid carried is due to the hemoglobin, the remainder being carried by the other buffer systems. The buffer value of the inorganic phosphate the authors show to be less than 1% of the total, while that of the separated serum is less than 5%. A revised value of 0.27 as a factor to correct for oxygen unsaturation in interpolating venous points is given by the authors. The isohydric absorption of 0.44 volumes per cent of carbon dioxid occurs with each volume per cent of oxygen unsaturation of the hemoglobin of the blood.

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**The Determination of the Titratable Alkali of the Blood.**

*Isidor Greenwald and Gertrude Lewman, J. Biol. Chem., 54:263, Oct., 1922.*

For this procedure 2 methods are suggested by the authors: (1) the gravimetric, using nitron, and (2) the volumetric, using titanous chlorid. For the first procedure, 5 c.c. oxalated blood is measured into a 50 c.c. volumetric flask and diluted with about 10 c.c. water. About 30 c.c. 1% picric acid solution is then added, with shaking, and the mixture is diluted with water to the mark. The mixture may be filtered in 30 minutes, or, if shaken frequently, in 10 minutes, or less. Then 30 c.c. filtrate is heated to boiling in a 150 c.c. Erlenmeyer flask, cooled in water, and titrated with 0.01 N NaOH, using 4 drops of 0.01% methyl red as indicator. After the end point has been reached, 4 drops of 0.01% phenol red are added and a second titration is made to the appearance of a definite orange color. Finally, 8 drops of 1% thymolphthalein may be added and a third titration obtained. The liquid is then strongly acidified with acetic acid, heated to boiling, and

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the picric acid is precipitated by the addition, from a dropping tube, of a 1% solution of nitron in 10% acetic acid. The precipitate is filtered out on a tared Gooch crucible, washed with water, dried at 110° for 1 hour, cooled, and weighed. If thymolphthalein has been employed, a correction of 0.1 mg. for each drop of 1% solution used is subtracted to allow for the amount of thymolphthalein carried down with the precipitate.

The molecular weight of the nitron picrate is 541. Theoretically, if each molecule of picric acid is neutralized by 1 molecule of NaOH, 1 mg. of nitron picrate equals 0.1848 c.c. 0.01 N NaOH. This is the value actually obtained by experiment with methyl red. Other factors must be used with other indicators. These factors are best obtained by titrating 5 c.c. portions of 1% picric acid with 0.01 N NaOH, using all 3 indicators in turn, then precipitating with nitron, weighing the nitron picrate, and calculating its value in terms of 0.01 N NaOH. It was found that 1 mg. of nitron picrate equals 0.1890 c.c. 0.01 N NaOH to phenol red and 0.1958 c.c. to thymolphthalein. From the alkali equivalent of the nitron picrate there is deducted the amount of alkali required to neutralize, to the corresponding indicator, the free acid in the sample. The difference represents the amount of alkali previously combined with protein or with carbonic acid in the blood. The results are then calculated in terms of cubic centimeters of 0.1 N NaOH per 100 c.c. blood, by dividing by 3 and multiplying by 10. The error is within  $\pm 1\%$  with methyl red and is less than  $\pm 2\%$  with the other indicators.

The second or volumetric method, using titanous chlorid, is of value when only a very small amount of blood is available. From 0.3 to 0.5 c.c. blood in a 0.5 c.c. Mohr pipet, graduated to the tip at intervals of 0.01 c.c. and capable of being read to 0.005 c.c. is measured into a 5 c.c. centrifuge tube, graduated in 0.05 c.c., and containing a few drops of water. The pipet is rinsed with this water and then with a little fresh water. Picric acid solution is added to make the final volume 10 times that of the blood taken, the tube is covered, shaken, allowed to stand and then centrifuged. As much of the supernatant liquid as can be obtained is pipetted off with a 3 c.c. Mohr pipet, graduated to the tip in 0.025 c.c., and delivered into a conical flask, 14 cm. high, 30 mm. in diameter at the bottom and with a neck 18 mm. in diameter, in which the free acid is titrated, using only methyl red (1 drop) with 0.005 N NaOH from a 2 c.c. buret, graduated in 0.01 c.c. Add 20 drops of concentrated sulphuric acid and insert a rubber stopper carrying an inlet tube which reaches nearly to the bottom of the flask, an exit tube, and a glass plug. While passing a stream of carbon dioxid from a generator or from a tank, heat to boiling, remove the glass plug and through this opening run in from a 10 c.c. buret 10 c.c. of approximately 0.05 N titanous chlorid solution. Replace the plug and continue boiling for 5 minutes. The solution should retain a pink color, indicating the presence of an excess of titanous chlorid. The flask is then cooled in water, the plug is removed, and the excess of titanous chlorid is titrated with an approximately 0.05 N solution of ferric ammonium sulphate. When the titration is nearly completed, 1/15 volume of 10%  $\text{NH}_4\text{CNS}$  is added and the titration continued to the appearance of a red color.

The stream of carbon dioxid is not interrupted until the titration  
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has been completed. The excess of titanous chlorid should require at least 2 c.c. ferric ammonium sulphate solution.

All 3 solutions are kept free from air in specially designed bottles. The ferric ammonium sulphate solution keeps well and need be standardized against picric acid only once. The titanous chlorid deteriorates slowly and should be checked daily against the ferric ammonium sulphate. Each millimol of picric acid requires 18 millimols of titanous chlorid; therefore, 1 c.c. 0.05 N titanous chlorid (or ferric ammonium sulphate) is equivalent to 1/360 millimol of picric acid or to 1/1.8 c.c. 0.005 N alkali. The amount of alkali required to titrate the free acid is subtracted from the alkali equivalent of the titanous chlorid used and the difference is multiplied by the appropriate factor to obtain the result in cubic centimeters of 0.1 N alkali per 100 c.c. blood. Results obtained by the methods described are unaffected by the presence of small amounts of oxalate or by the degree of saturation of the blood with oxygen or with carbon dioxid.

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**The Chlorin Distribution between the Blood Corpuscles and the Plasma. The Influence on It of Carbon Dioxid Tension.**

*Z. Dische, Biochem. Ztschr., Berlin, 131: 596, Sept. 16, 1922.*

The assertion of Falta and Richter-Quittner that in man and in all of the species of animals examined by them the blood-corpuscles under normal conditions contain no chlorin or only slight traces of it was doubted by different authors. Creveld believes that Falta's source of error lay in the fact that in taking the blood the escape of carbon dioxid from the plasma was not prevented. This caused a migration of chlorin ions out of the corpuscles into the plasma. When therefore the corpuscles were found free of chlorin it does not prove that in the circulating blood they were really free of chlorin. Experiments made by Creveld on this point were retested and it was found that in normal individuals the blood-corpuscles are free of chlorin both in the circulating blood and in blood that has been removed from the vessels, allowing the escape of carbon dioxid. But in certain diseases, particularly kidney diseases and hypertonia, the blood-cells contain considerable amounts of chlorin whether they were taken with paraffin occlusion of the blood-vessels or not, a condition that in Dische's experience is accompanied by swelling of the blood-vessels. But the chlorin content of the serum in these cases is about the same as normal.

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**Blood Tests and Kastle-Meyer's Reagent.**

*L. Servantie, J. de méd. de Bordeaux, 94: 636, Oct. 10, 1922.*

Kastle-Meyer's phenolphthalein reagent is unreliable for the detection of blood, as it gives a positive reaction if as little as 1 part of copper in 100,000,000 is present. In the author's experience, enough copper was dissolved by the action of the acid gastric juice on the brass tip of a sound to give a positive reaction. Water distilled in a copper apparatus and preserved in a glass container with a metal faucet gave a faintly positive reaction.

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**The Use of the Hopkins Tube in Standardizing Cell Suspensions.**

*E. E. Eckér and H. Maynard Rees, J. A. M. A., 79:1685, Nov. 11, 1922.*

The Hopkins tube is of the centrifuge type, of 10 c.c. capacity. The end has been drawn out for about 2.5 cm., so that the bore is of capillary diameter. This portion is graduated in hundredths of 1 c.c., from 1 to 5 hundredths, and is stout enough to withstand the pressure of centrifuging without a special holder. It is advisable carefully to prepare a preliminary standard suspension from which the volume of precipitated cells can be determined. Proper amounts or dilutions can be roughly figured so that the sedimented corpuscles will not exceed in volume the graduated tip. Two cubic centimeters of a 5% suspension of sheep erythrocytes will give just sufficient cells to fill the capillary end of this tube. Repeated centrifugations with the same suspensions, with the same speed and time, have given the authors constant results which can be read accurately to one five-hundredth of 1 c.c. Uniform suspensions can later be readily made. If a suspension yields a certain volume of cells in excess, the corresponding volume in salt solution is added; and, if too low a volume is found, the concentration can be increased by the addition of washed full blood. The authors have obtained excellent results with the use of this tube.

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**The Blood Count. Improvements in Method.**

*A. Cecil Alport, Lancet, London, 203:756, Oct. 7, 1922.*

Because of the many sources of error in taking blood counts, despite great care at each step, it is impossible to obtain really accurate results. There must be accurate contact between the cover slip and the counting chamber. To ensure this Newton's rings should be present all around the cover slip. The author suggests the use of a cover glass 0.375 mm. thick to avoid the buckling frequent with a thinner slip and consequent uneven distribution of the cells. With a thick cover glass it is necessary to use a No. 18 compensating eyepiece and a 2/3" objective. With this method the count is more accurate, as shown by a comparison with counts made by the usual method in a series of 150. Besides the advantage of more accurate contact, much time is saved by the greater ease in placing the thick cover slip.

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**Refractometry or Counting Blood-Cells for the Determination of Changes in the Amount of Blood.**

*Richard Prigge, Deutsch. Arch. f. klin. Med., Leipsic, 140:165, Sept. 5, 1922.*

In studies of processes of exchange between the blood and tissues, extrarenal genesis of edema, etc., frequently mere determinations of

changes in the amount of blood are made. Bauer and Aschner regard the possible albumin exchange between the blood and tissues as unimportant. Nonnenbruch rejects the use of the refractometric method for following up changes in blood concentration and Magnus assumes that under certain conditions albumin may pass through the vessel walls. His experiments are based on calculations with an average value for the relative blood-cell volume, the results of which are somewhat fallacious. There is a rather important reason against the use of the refractometric method of serum albumin determination. For even if the amount of albumin of the serum is constant, yet from changes in the percentual serum albumin content conclusions can be drawn only as to changes of the total amount of serum, not as to changes in the total amount of blood. Direct conclusions cannot be drawn as to processes of exchange between the blood and tissues, as processes of exchange between the serum and blood-cells must also be taken into consideration. It is safer to calculate the changes in the total amount of blood from the number of the morphologic elements, when it is borne in mind that the total amount of blood before and after an operation are inversely proportional to the number of erythrocytes contained in a unit of volume. Conclusions can be drawn only as to the plasma; then from the proportion of the amount of plasma to that of blood-cells, further deductions can be drawn.

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**The Relative Volume of Corpuscles and Plasma, and the Relation of This to Hemoglobin Percentage and the Number of Red Blood-Corpuscles.**

*J. M. H. Campbell, Brit. J. Exper. Path., London, 3:217, Oct., 1922.*

To venous blood was added solid potassium oxalate sufficient to give a 0.5% solution. Sixteen subjects with no anemia were used as normal controls. The hemoglobin percentage was determined generally in duplicate by a specially standardized Haldane-Gowers hemoglobinometer. The red blood-corpuscles were counted with a Burkner-Zeiss hemocytometer—at least 2000 in each case. To determine the relative volume of corpuscles the blood was well mixed and into it capillary tubes were dipped, the tubes being of definite length; when the blood had risen to near the top the upper end of the tube was sealed in a flame. The 6 capillary tubes were then centrifuged for 15 minutes when the heights of the corpuscles and of the whole blood were measured, the former expressed as a percentage of the latter, the average results being recorded. It was found that the corpuscular volume varies almost directly with the hemoglobin percentage. There is little change in the concentration of hemoglobin in the corpuscle in various pathologic conditions (secondary anemia, chlorosis and pernicious anemia). The term "volume index," which is the ratio of the corpuscular volume to the number of red cells, gives a measure of the relative size of the red cells. The size depends almost entirely on the hemoglobin content, so the color index is a rough guide to the size of the average red cell. The author observed that in pernicious anemia



the average cubic contents of each red cell is increased by about 30%. In secondary anemias and chlorosis it was diminished by about 30%, while in polycythemia it was unchanged.

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**The Diameters of Red Cells in Pernicious Anemia and in Anemia Following Hemorrhage.**

*Cecil Price-Jones, J. Path. & Bacteriol., Edinburgh, 25:487, Oct., 1922.*

By a method previously described by the author, dried blood films were prepared and the diameters of 500 red cells in each were measured to 0.25  $\mu$ . The mean diameter of 500 cells was taken to represent the mean diameter of the red cells for any specimen of blood. Blood films were made from 20 healthy persons, 20 patients with pernicious anemia, and 10 with anemia following hemorrhage. From the author's tabulated and graphic data it appears that the mean diameter of the red cells in pernicious anemia is greater than that in healthy persons; the smallest mean diameter of the pernicious anemia cases is equal to the largest mean diameter of healthy persons. The mean diameter in cases of anemia following hemorrhage is smaller than that in healthy persons, the largest being less than the average mean diameter of the healthy persons. The mean coefficient of variation of the red cells in the pernicious anemia cases was found to be more than twice the mean coefficient of variation in the healthy persons, and the smallest coefficient of variation of these cases is greater than the largest coefficient of variation of the healthy persons. The mean coefficient of variation of the red cells in the hemorrhage anemia cases is half as large again as that in healthy persons, the smallest being equal to the largest coefficient of variation in the healthy persons.

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**Clearer Demonstration of Basophil Erythrocytes in Thick Drops of Blood.**

*Helmuth Schreiber, Deutsch. med. Wchnschr., Leipsic, 48:1337, Oct. 6, 1922.*

It is often difficult for the inexperienced individual to recognize immediately polychromasia and basophil dots in the ordinary thick drop. This is made easier by vital staining. The author has used the combined brilliant-cresol-blue Giemsa stain recommended by Schilling on thick drops and has found extraordinarily sharp pictures. In this method, the advantages of vital staining are combined with good preservation of the specimen.

Schilling uses slides previously prepared with the stain for the smears; lets the vital staining of the fresh smear of blood take place in a moist chamber; and dries the smear, which is then treated as usual. After the slide is thoroughly cleaned, as much of the brilliant-cresol-blue solution is put on it with a glass rod as is necessary to give it a dark violet tone. Then a moist chamber is made of 2 Petri dishes. The floor of the dishes is covered with filter paper and this is moistened.

In the lower Petri dish, before the chamber is closed, are placed a few broken slides on which the prepared slide is to lie. From the finger tip or still better from the lobe of the ear of the patient a drop of blood is now allowed to fall on the prepared slide and it is spread out with a needle until it is the size of a penny. The blood mixes immediately with the stain and takes on a greenish tone. Then the slide is at once laid in the moist chamber which is opened only for a moment. After 10 minutes the slide is taken out, is allowed to dry in the air well protected from flies and is now stained like any ordinary specimen with Giemsa stain. If there is polychromasia or basophil punctation it appears quite sharply as fine, generally torn dark blue nets or as coarse dark blue points on the bright blue background. In judging their strength, a different sort of measurement is to be applied than with the ordinary stained blood drop, for they seem to be much more numerous and thicker. With this method of staining it is easy to recognize polychromasia and basophil punctation in thick drops.

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**Reticulosis; Increased Percentage of Reticulated Erythrocytes in the Peripheral Blood.**

*Edward B. Krumbhaar, J. Lab. & Clin. Med., 8: 11, Oct., 1922.*

The author considers the cytologic status of reticulated or skeined erythrocytes. Having been interested in these cells for a number of years, and having tried various methods for demonstrating the reticulum of the cells, he has found the method described to be the simplest and most satisfactory for clinical use.

A stock 0.3% solution of brilliant cresyl blue (Grubler) in normal saline is prepared in quantity sufficient to last for several months, filtered and kept in the ice box to inhibit molds. Before using, it is diluted with 4 parts of a 2% sodium oxalate solution in normal saline to 1 of the stock stain and in this strength it is useful for several days. If Grubler's stain is not available, a 1:2000 aqueous solution of Janus green is recommended as a stock solution and similarly diluted before using. From a freely flowing cut, a drop of blood is sucked into a pipet and quickly diluted about 1:10 with the stain. After standing 10-15 minutes, this is well shaken and a wet coverslip preparation made from the contents, ringed with vaselin, and examined with the oil immersion lens. Especial care should be taken to prevent crenation, which makes recognition of the reticulum more difficult and perhaps inhibits the entrance of the stain into the cell.

An opportunity was offered to study the percentage of reticulocytes in dog's blood during the production of experimental plethora by means of daily transfusions from dog donors over periods of several months. In 4 dogs studied in this manner, the reticulocytes either vanished entirely or diminished to such an extent that the possibility must be considered that they had been introduced with the slightly anemic donor's blood. In 1 animal, though the transfusions were continued without interruption, the hemoglobin fell from 133 to 13% in 23 days, and the erythrocytes from 10,000,000 to 650,000 per cubic millimeter. After

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10 days, when the hemoglobin had reached 50%, the reticulocytes began to increase and normoblasts and megaloblasts appeared in the peripheral circulation. With gradual recovery from anemia, the reticulocyte count fell again until after 4 months it had reached almost normal level.

The reticulocyte count in normal adults is considered abnormal only if more than 1% or less than 0.1%. In infants, the author has not found any counts to exceed 5% at birth, or after the first 24 hours to exceed 3%. By the end of the first week of life, practically normal levels are reached, and thereafter the normal infant's reticulocyte picture is the same as that for adults. Variations in the reticulocyte percentage in disease naturally depend on the intensity of the demand and the capacity of the bone-marrow to respond. In pernicious anemia, while there is usually a reticulosis of 2-5% during blood crises, this may rise to 10 or 15%; in periods of regression these cells may be completely absent. In the 2 forms of hemolytic jaundice, the reticulosis is out of all proportion to the severity of the anemia, being customarily as high as 10 or even 20%. The reason for this, which is of diagnostic import, has not been determined. In secondary anemias, the reticulosis is roughly proportional to the severity of the anemia. It is present in the purpuras, and in true polycythemia is said to be increased. In aplastic anemia and other forms of anemia due to decreased blood formation, these cells are diminished (reticulopenia) or absent.

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**An Attempt at Improving Blood Examination for Leukocytes.**

*Claus Schilling, Deutsch. med. Wchnschr., Leipsic, 48:1337, Oct. 6, 1922.*

The defectiveness of the method of blood examination in rapidly dried blood smears in which a large but not uniform percentage of the different types of white cells are destroyed, caused the author to suggest the following improvement: In a cylindric tube with a pedestal he places 5 drops of the following solution: cyclamin 0.04 gm., sodium chlorid 0.8 gm., sodium citrate 1.0 gm., distilled water 100 gm. Cyclamin is a preparation belonging to the saponins and extracts erythrocytes in high dilutions to such an extent that their shadows do not disturb the microscopic picture but the white blood cells are not changed in the time necessary for examination. In the laked blood all the other constituents except the erythrocytes are clearly visible. From a small wound, preferably in the lobe of the ear, 3-4 drops of blood are added to the 5 drops of solution; after about 10 minutes the blood is laked. The cyclamin solution can be kept only about 14 days; after that it does not act rapidly enough. A large drop of the laked blood placed on a slide, and a large drop of stain are mixed by being blown together with a capillary pipet and covered with a cover glass; this is fixed with 4 drops of balsam and looked at with the immersion lens. Dilute methylene blue is the stain used. Also azure 1 (Grubler) gives a good nuclear stain in a dilution of 1:500. The method unites the advantages of the thick drop (many leukocytes in one field) and a good nuclear staining.

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**The Azure-Granule Cells and Their Normal Qualitative Blood Picture by Arneth's Method.**

*Arneth and Fritz Stahl, Ztschr. f. klin. Med., Berlin, 95:201, Sept. 15, 1922.*

The small and large lymphocytes, mononuclears and transition cells are included under the name lymphoid cells and classified according to the nuclei and azure granules by Arneth's principle. They were counted in 10 normal men. Tables show the distribution of the individual forms of lymphoid cells with reference to azure granulation. It was found that about 18% of the lymphoid cells show azure granulations, chiefly the moderate sized lymphocytes. The older cells (division into W, T, and P-cells and transition forms) show an increasing tendency to granulations. Two other tables show whether the granulations are fine, medium, large or mixed, and whether many or few granules are present. The fine granulations predominate, large ones are rare. Coarsely granular and mixed granulations were most frequent in the medium-sized lymphocytes. Finely granular and medium-sized granulations were found mostly in the small and large lymphocytes, as well as in the monocytes. Monocytes and transition forms had almost exclusively fine granulations. On the whole the size of the granulations increases with the age of the cell. Few granules are found in the small lymphocytes, they are more numerous in the W-cells, particularly so in the medium-sized W-cells. The authors from their own findings come to the conclusion that the granules are a manifestation of a definite function of the lymphoid cells. If necessary, any lymphoid cell can form granules, but there may be decreased production or even total disappearance of the granules.

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**Basophil Substances within Polynuclear Leukocytes.**

*J. Sabrazès, Arch. d. mal. du coeur, etc., Paris, 15:643, Sept., 1922.*

Basophil granules, contained within polynuclears, have been reported in the presence of pneumonia, erysipelas, diphtheria and other infections. The author and his associates have found them, more recently, in malaria, rabies and small-pox.

These inclusions are rarely present in normal blood, occurring especially during infections. A high percentage may indicate occult infection. In a case of Vaquez' disease, the polynuclears containing the basophilic granules numbered 16%, careful investigation showing the presence of a tuberculous process.

For detecting the granules, the author employs the droplet method, mixed with 1:500 methylene-blue, or thin, well-dried smears. Good preparations are obtained by fixing with alcohol and staining with borated methylene-blue. The granules probably constitute remains of the original basophil cytoplasm of the cell, which develops with abnormal rapidity. Similar granules sometimes occur in red cells. The basophil granules must not be confused with nuclear granules observed in various pathologic conditions, but rarely during infections. The nuclear granules are rounded, 1 or 2 are present near the nucleus, and they take

nuclear stains. The basophil inclusions stain with pyronin, the nuclear fragments do not.

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**The Nuclear Morphology of the Myeloblasts and the Neutrophil Leukocytes.**

*R. Hammerschlag, Frankfurt. Ztschr. f. Path., Munich, 28:21, No. 1-2, 1922.*

The author's observations on pleomorphism of the myeloblasts and neutrophil leukocytes have confirmed and extended those on the salivary corpuscles, eosinophil leukocytes, erythroblasts and transitional forms. In the large nuclei of the myeloblasts it is possible to observe those processes which initiate pleomorphism. In the myeloblasts, as in the myelocytes and transitional forms, the chromatin is withdrawn from a part of the nuclear membrane so that there are surfaces which either contain a pale chromatin or are entirely free of chromatin. These places are bounded by a zone of chromatin which exceeds in breadth and intensity of color the chromatin of the rest of the nucleus. This deeply colored chromatin is generally rectangular in form and involves many nuclei or a part of the nucleus indented on two symmetrical sides. Such ostia were first seen in lymphocytes where they were surrounded by sharp lines. In larger basoplasmic cells the lines are broader and in some places provided with small processes which radiate toward the ostium as well as, for short distances, toward the other nuclear surfaces. They are not entirely continuous, but are composed of nodules and threads. Sometimes, however, they become thicker, forming uninterrupted rhomboidal lines, which in a certain position of the nucleus seem to be saddle-shaped. These ostia are in many places crossed by heavier chromatin lines, which later disappear or remain as small peaks in the nucleus. In the neutrophils they persist in two or more places, so that the number of nuclei in the polynuclears is determined by them. The ostium is the place at which the nucleus opens. It is not always clear whether the ostium surface breaks off abruptly and disappears or whether it sinks in slowly. Nor is it always possible to say whether the depression within the ostium is a part of the surface of the latter or a part of the inside of the nucleus. Only this much is certain that so soon as the walls of the ostium begin withdrawing from one another, the ostium completely disappears. In the ostia of nucleoli the conditions are the same; in the "spectacle" ostia the separation is best seen at that place where the connecting bow runs. Before the myelocyte nucleus opens, that is before the dilatation of the ostium space, the contents of the nucleus may have escaped through the ostium. The nucleus is first a deeply indented sphere, then it becomes stretched out more like a bowl or a groove, and the threads which bridge it over are stretched, then torn and finally dissolve. The inner surface is in most cases very clear, poor in chromatin or with no chromatin at all, but sometimes the structure is the same on the inner and outer surfaces.

The myeloblasts retain their ovoid outlines and accomplish their changes in the narrow zone of plasma. In the myelocytes with their relatively small nucleus there is an infinite abundance of forms. The groove opens and may undergo a rotation of 180°; it may become



inverted, stretched out into a band-shape and very narrow. It assumes a polynuclear appearance from folding and manifold twisting. Also in these polymorphic neutrophil leukocytes, rings may be formed by disappearance of the central part of the nucleus. When the threads inside the ostia hold the nuclear remnants together after disappearance of the ostia, the design for the polynuclear leukocytes is thus given. If the threads are preserved for a long time at two opposite points of the nucleus, a nucleus with an opening is formed, and this may be held together at its tips by a pair of threads or by a bundle of threads. These thread systems develop from thin membranes. In the bone marrow there are, especially in microgeneration, nuclei which separate like nut-shells and are only held together at one point by a thread. Such nuclei are not preceded by any ostium formation, but the nucleus is broken up into two or, in rarer cases, several pieces. The chromatin structure of the myeloblasts is of lymphoidocytic, leptochromatic or cribriform structure which in the oldest ones (leukoblasts) is transformed into a large-meshed network of stiff chromatin, so that in the myeloblasts the chromatin structure is leptochromatic and trachychromatic.

The myelocytes have a manifold chromatin structure which is generally composed of fine threads, coarse or fine nodules. The nodules are sometimes stretched out until they have a striped arrangement, and the long narrow bands are sometimes reduced to transverse stripes and nodular threads of chromatin. The rings are generally provided with parallel, markedly transverse chromatin bands. The chromatin structure is similar in the polynuclears. The bands of the myelocytes consist of oxychromatin and are found in polymorphs as well as in polynuclears. Where they appear they suppress the basic chromatin, destroy its structure and take up its masses in their meshes. The bands emerge from the nucleus in the form of equally broad, pale bands, which increase successively in number and density. The basic chromatin withdraws first into the spaces between the bands, but soon it can be seen that the basic chromatin, together with the nuclear membrane, has disappeared. The bands have thus taken possession of the whole nucleus, and made a bundle of oxychromatic bands out of it. These bundles may for a time preserve the old outlines of the nucleus, but they may assume manifold forms. This formation of bands may begin at any phase of pleomorphism, both in myelocytes and in polynuclear leukocytes with four fragments. The bundle may be dense or it may be scattered. The author believes that the nucleus undergoes radical changes in pleomorphism, that the change of form is preceded by a change in its content, a structural change of the basic and oxychromatin, that the membrane is ruptured and that an open bowl or groove-shaped nuclear body undergoes all the further changes.

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#### **The Primary Wandering Cell.**

*Giovanni Di Guglielmo, Haematologica, Naples, 3:469, Sept., 1922.*

Embryologic research on mammals led the author to formulate these general conclusions: The blood of the embryo, in the prehepatic  
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stage, contains neither hemocytoblasts nor lymphocytes comparable to the corresponding elements in the adult. The cells with pronouncedly basophilic protoplasm occasionally seen in some preparations are lymphoid megaloblasts, and not leukocytes; in other words they are transition forms between clasmatocytoid hemohistoblasts and primary erythroblasts. The true primary wandering cell is therefore not a lymphocyte, basophilic megaloblast nor transitory hemocytoblast, but a hemohistoblast, i.e. a histocytic, clasmatocytoid cell, as yet not recognizable morphologically, from which are derived, in successive stages quite readily to be made out, the basophilic megaloblasts.

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**The Lymphoidocyte and the Türk Cell. Their Hematologic Relationships and Clinical Significance.**

*J. C. Matthews and C. V. Pearson, Lancet, London, 203:909, Oct. 28, 1922.*

This work analyzes Knyvett Gordon's theory that the presence of lymphoidocytes in bacterial endocarditis and other serious conditions is of ominous prognostic significance. To get uniform results the films were stained by a method suggested by Gordon: (1) Jenner's stain undiluted, 2 minutes; (2) Jenner's stain diluted (1:20) with distilled water, 5 minutes; (3) Giemsa's stain, diluted (1:20) with distilled water, 20 minutes; (4) distilled water, 10 minutes; (5) blot, dry in the air, smear with cedar oil and examine. The advantages of this method are uniform and strictly comparable results, clearer definition of the structure of the nucleus than with the shorter methods, and vigorous differentiation of the granules of the cytoplasm, not only of the eosinophilic and basophilic granules, but also of the azure granules of the lymphocytes and other mononuclear cells. The lymphoidocyte, the primordial mother cell, has cytoplasm which forms a narrow rim around the nucleus and stains a moderately deep blue; the nucleus has a fine chromatin network which stains much less deeply than that of the lymphocyte; 3 or more nucleoli can be distinguished, and sometimes a small number of fine azure granules can be made out in the cytoplasm. In a table are set forth the differential characters of the lymphoidocyte, Türk cell, lymphocyte and erythroblast, which are somewhat similar in type. The authors examined blood films from 225 cases, including 213 nonleukemic and 11 leukemic cases, and 1 case of Jaksch's anemia. In the 213 nonleukemic cases not a single lymphoidocyte was found. In the 11 leukemic cases they were present in varying numbers, 2-87%. In the remaining case there were cells representing all stages of transition from the lymphoidocyte to the normal red blood-cell. From a summary of the findings, it is evident that the results are directly contradictory to those of Gordon, at least in regard to the lymphoidocyte. The lymphoidocyte was not found in infective endocarditis or any condition other than disease of the hematopoietic organs in which their occurrence is already recognized. The Türk cell has characteristic features and is occasionally found in normal blood. Its presence in large numbers is probably pathologic and points to the existence of a generalized bacterial infection. It has only an indirect bearing on prognosis.

## 1f. PATHOLOGY

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**The Pathology of Inflammations (with Emphasis upon Sepsis).**

*Robert A. Keilty, New York M. J., 116:588, Nov. 15, 1922.*

Pathology represents a battle between the host and an invader which is constantly being carried on with more or less success on the part of the host. The character of the invader and the barriers of the host are fixed basically. The principles of an invasion will be pathologically the same regardless of the site of the reaction. They may be considerably influenced by the site selected but their pathology and rational treatment should be identical. An inflammation is a disease in which there is an acute, a chronic or a specific reaction against a stimulus, frequently bacterial, responsible for cell and group unit changes in the body, with an altered physiology and subjective symptoms modified by the site of the invasion. An invasion is the movement of the stimulus through a portal of entry, with or without a reaction or a focus of infection at this portal. The reactions set up depend upon the character of the stimulus or injury responsible for them. There is no disease which produces a foreign or new type of cell but diseases produce a new grouping of cells and of function.

In sepsis an invasion with a pus-producing agent is necessary. This is a fixed constant. The agent may invade directly or it may be secondary from a portal of entry or a focus of infection. After the invasion there is found the classical, clinical group: rubor, dolor, calor and tumor. The first reactions are blood vascular in character, due to the bacterial toxins. The blood-vessel walls dilate, there is a separation of the endothelial cells of the capillaries with the escape of fluid. As the walls dilate the current of blood slows down, the red blood-cells become sticky and stasis of the current occurs. This may go on to actual thrombosis and complete obstruction in the capillaries involved. With this the leukocytes marginate to the walls of the vessels and by their ameboid movement emigrate through the wall and toward the point of irritation. A pus cell is a dead or dying polymorphonuclear leukocyte acting as a phagocyte. Reparative reaction or healing by granulation is a replacement process and cannot be fulfilled until every particle of the suppurative process has been completed. The careful application of this principle utilized by the French during the war and known as débridement hastens and shortens an otherwise indeterminate repair and recovery.

Wherever pus occurs early incision and drainage are indicated. Great care should be exercised not to go beyond nature's lines of defense and spread what would otherwise be well localized. The common practice of squeezing an abscess area is almost criminal. After thorough drainage, efforts at sterilization are to be inaugurated, properly prepared Dakin's solution or dichloramin-T being the best agents to date. After sterilization the practice of débridement, followed by efforts at closure and granulation by primary union, offers the best course for early and complete recovery.

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**Premature Ossification and Its Relation to Chondrodystrophia Fetalis.**

*Max Budde, Frankfurt. Ztschr. f. Path., Munich, 28:461, No. 3, 1922.*

In premature ossification of the epiphyseal line it is a question why the cartilage-marrow canals of the epiphysis and diaphysis unite too early, thereby causing the indifferent layers of cartilage bounded by them to be given over to calcification and robbed of further capacity for cell division. Is it a process which affects the whole cartilaginous symphysis at the same time and to the same degree, or a process which develops at a circumscribed place and progresses in all directions, and causes a typical shape of the joint end? In the cases described by the author the epiphysis was surrounded by the diaphysis like a husk, and the boundary line which was still distinguishable in the frontal picture represented the 2 sides of a roof, the ridge of which lay about in the middle and corresponded to the place of the first fusion of the 2 parts of the bone. When at a certain point the growth in length stops from fusion of the shaft with the epiphysis, the parts of bone around this point are influenced by it, as they widen out first toward the side and finally toward the joint, but in oblique lines converging toward the fixed point. The result is that the total amount of growth is scarcely decreased but that it is forced into false paths, i.e. growth goes partially toward the side and does not take place wholly in a longitudinal direction, and furthermore, that the zone of resting cartilage takes a descending course toward the epiphysis.

The premature synostosis according to M. B. Schmidt is due to premature using up of the cartilaginous matrix and defective proliferation of the cartilage, and is as a rule only a partial manifestation of a general disease of the skeleton. Local injuries may also be factors, such as acute and chronic osteomyelitis, traumatic separation of the epiphysis and chronic inflammation of the joint. The action of force need not however be especially intense. Lexer distinguishes 3 vessel zones at the ends of the joints, the diaphyseal, the metaphyseal and the epiphyseal. The two latter are connected with one another by rami perforantes. With advancing age the metaphyseal vessels undergo retrogression and unite with the epiphyseal and diaphyseal ones. Their character as end-arteries is lost and gives way to the formation of anastomoses. It may easily be deduced from this that on tearing of the metaphyseal vessels by crushing of the spongiosa, the epiphyseal vessels, by dilatation of the few connecting branches, take their place. Along the connective tissue which accompanies them osteoblastic material advances from the epiphysis, thus initiating the premature synostosis. Also at the posterior insertion of the crucial ligament, at the posterior circumference of the head of the tibia, on overextension this same process of separation of bone continuity may occur. If this causes disturbance of growth in the affected area, the whole upper epiphysis of the tibia must seem to be displaced backward. In rickets there is a uniform backwardness in the growth of cartilage in the resting zone. But preliminary synostosis between the shaft and epiphysis is much more frequently encountered in a congenital skeletal

disease, chondrodystrophia fetalis. There is a preliminary ossification of the cartilage lines of the base of the skull. But in contrast with this, in some cases these lines remain open without proliferation of cartilage, sometimes indeed the base of the skull remains in almost a cartilaginous condition with only very slight ossification.

Often the ossification centers of the bodies of the vertebrae and the vertebral arches fuse prematurely, so that an extreme frontal stenosis of the spinal canal occurs. In absence of the anlage for the epiphyseal ossification center, irregular ossification foci extend from the metaphysis toward the epiphyseal cartilage. Epiphyseal vessel buds are lacking and are replaced by buds from the metaphysis. If this occurs in abundant measure an ossification center develops, which, however, is inseparably connected with the diaphysis. This initiates the synostosis and shortening of growth. Or it may be that the vessels cannot penetrate to any great degree from the diaphysis. They then seem to be increased in number and pressed together, and the epiphysis remains for a long time cartilaginous, finally obtaining an ossification center either from the shaft or from its own epiphyseal vessels.

The boundaries between the bone and cartilage in the ribs are characterized by the fact that they have thickenings which are sometimes due to the cartilage, but more frequently the bony part of the rib surrounds the cartilaginous part like a beaker. This is explained by the fact that in the middle of the rib the cartilage is most degenerated and answers least with cell increase to the growth stimulus coming from the vessels. The synostosis of the base of the skull and the vertebrae is to be explained by the fact that there is only one center of ossification and the ossification of the whole cartilage region takes place from it. The first beginning of the disturbance must be at a much earlier stage, that of the primordial cartilage, where a cartilage anlage develops from a single vessel bud. The periosteum stripe is a characteristic finding in chondrodystrophy; it is found always or at least very frequently in the malacic and hypoplastic forms, but only rarely in the hyperplastic form. After the insertion of this a limit is fixed to the growth in length; the bone grows toward the opposite side, which causes curvatures. According to M. B. Schmidt and Dietrich it presents a cartilage-marrow canal with an especially abundant and well developed connective tissue.

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### **Parathyroid Tumors and Their Relation to Osteomalacic Bone Disease.**

*Burkart Strauch, Frankfurt. Ztschr. f. Path., Munich, 28:319, Nos. 1-2, 1922.*

Under the collective name of osteomalacic bone disease are included rickets, including late rickets, osteoporosis, the puerperal, senile and famine forms of osteomalacia and osteitis fibrosa. Erdheim first discovered the changes in the parathyroids in osteomalacic disease. They were chiefly proliferations in the parathyroids. The author reports a case of parathyroid tumor with osteomalacia at the same time. On autopsy a parathyroid tumor was demonstrated that was shown by histologic examination to be a true blastoma. In the case described,

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apparently the patient had only one parathyroid. Even under normal conditions this would have been seriously overburdened with work. The bone disease caused still more overexertion and hyperplasia. Further functional demands brought about decompensation and tumor-like degeneration from the fact that the functional stimulus set free an excess of force.

Excess of growth is caused by overtaking of function. The hyperplastic tumors which appear at the same time as bone disease all seem to belong to the group of hyperplastogenic blastomas, while the pure adenomas seem to be representatives of dysontogenetic tumors. The tumors generally found are representatives of the second group. Hypertrophies of the prostate, adenomas of the liver in cirrhosis, and myomas of the uterus belong to the latter. In the parathyroid tumors there is a difference in the process of compensation which is greater in quantity and quality than in these tumors. Therefore the name parathyroidomas may be used for them. Positive bone findings in mother-cell adenomas have not been described in the literature. Severe bone softenings do occur without parathyroid tumors but the opposite condition, hyperplastic tumor without bone changes, has not been definitely demonstrated. The fixative function of the parathyroid bodies is said to be the neutralization of one of the acids which destroys calcium. But no influence of its increased activity on the course of the disease was ever observed.

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**The Occurrence of Lymphadenoid Tissue in the Normal Thyroid and in the Thyroid That Has Undergone Goitrous Changes.**

*Elisabeth Hecker, Frankfurt. Ztschr. f. Path., Munich, 28:96, Nos. 1-2, 1922.*

Simmonds first demonstrated the occurrence of lymphatic foci in the normal thyroid gland; these had previously been demonstrated in goiter. Of 1000 thyroids examined at autopsy 5% were positive on this point, chiefly after the thirtieth year, while there were no lymphatic foci in children or new-born. The female sex was especially affected. Of 101 cases of goiter von Werdt found not less than 80 with lymph follicles or abundant accumulations of lymphocytes; in basedowian goiters he found this much more rarely. That the tissue atrophy caused by mechanical, chemical or infectiotoxic action plays the chief part as asserted by Werdt, Simmonds refutes by pointing out that the lymphatic structures are more frequent in basedowian goiters than in the diffuse or nodular forms, although the nodular ones have more atrophic tissue. In the basedowian thyroids the foci are quite irregularly distributed; sometimes they are in the gland lobes themselves, sometimes in the interstitial tissue, sometimes just beneath the capsule, generally without recognizable relation to the atrophied gland substance. In thyroid atrophy in senile or chronically cachectic persons the foci are not more frequent. In cases of severe atrophy in cretinism the change is quite normal.

The author's material was surgical with 3 exceptions and included 33 nonbasedowian goiters (5 with lymphadenoid tissue), 31 basedowian  
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goiters (19 with lymphadenoid tissue), and 56 normal thyroids (of which 7 were affected), the proportions being 15.1%, 61% and 12.5%. In the normal thyroid accumulations of lymphocytes were found only in women. Probably a mutual relationship between the thyroid and ovaries causes this, since the lymphadenoid tissue was found only in sexually mature women.

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**The Pathologic Anatomy of the Hypophysis. Relation of Pluriglandular Sclerosis to Hypophyseal Cachexia and Adipositas Hypogenitalis.**

*Bernhard Veit, Frankfurt. Ztschr. f. Path., Munich, 28:1, Nos. 1-2, 1922.*

Falta calls that condition a pluriglandular sclerosis in which a pathologic process, which is probably infectious but cannot be any more definitely defined, affects several endocrine glands at the same time and leads to extreme sclerotic atrophy and thereby to signs of loss of function of these glands. Generally the thyroid, sexual glands, hypophysis and suprarenals are affected. There are then more or less pronounced symptoms of hypothyroidism, late eunuchoidism and hypophyseal insufficiency combined with a syndrome similar to that of Addison's disease. A specially noteworthy symptom is a cachexia which develops irresistibly to a high degree. The clinical symptoms are those of disease of the individual glands.

Pluriglandular sclerosis is closely related to Simmond's cachexia. In the former there is, according to Falta, a progressive degeneration of the whole endocrine gland system, while in the latter there is a primary injury of the hypophysis, fibrous atrophy of the anterior lobe, followed by secondary changes in the thyroid, suprarenals and genital glands; the cause is probably the embolic processes in the hypophysis, which Simmonds says are not unusual, but it may also be basophil adenoma and, according to Schlagenhauser, tuberculous processes. Except atrophy of the hypophysis the only etiologic factor in Simmonds' cachexia is splanchnomicria with normal histologic findings. According to Bernard Fischer, adipositas hypogenitalis or dystrophia adiposogenitalis occupies a position between these 2 diseases. Anatomically there is an injury of the nervous part of the hypophysis generally caused purely mechanically by pressure. There is not necessarily any new growth of the hypophysis but, according to Pick and Strada, there is always tumor formation in the region of the infundibulum or the pedicle of the hypophysis. The endocrine glands are small but intact.

The author describes a case of endocrine gland sclerosis with autopsy findings: All the glands of internal secretion were atrophied, the genital glands most so, then the suprarenals and thyroid; there was less pronounced atrophy of the hypophysis and parathyroids, and the parenchymatous organs also showed induration which was most pronounced in the lungs. There were also atrophic processes in the bones, which is in harmony with the findings of Edelmann and Landsteiner, and xanthomas in several places. These latter may be interpreted as Umber interpreted them, as an externally visible symptom of degenerative processes in intermediate metabolism or as a

constitutional anomaly. Histologically there was slight injury of the spleen, liver and kidneys in the form of simple atrophy; the pancreas was practically normal and there were pronounced cirrhotic processes in the lungs. A progressive process of sclerotic atrophy was to be seen in the thyroid, more so in the suprarenals, still more so in the testicles and prostate. The parathyroids presented an embryonic picture. In the hypophysis the complete lack of chromophil cells in the anterior lobe suggested the fetal type according to Erdheim. In the posterior lobe, pars intermedia and pedicle, there were pronounced sclerosis and small accumulations of pavement epithelium which, however, were normal and are not to be regarded, as Erdheim thought, as precursors of pavement epithelium carcinoma. The progressive sclerosis of the endocrine glands was initiated by the disease of the hypophysis, and the latter has a controlling, or at least a regulating, position in the blood gland system. The failure of hypophysis function must, therefore, give rise to that symptom complex which is called multiple endocrine gland sclerosis or, according to Claude and Gougerot, insufficiency pluriglandularis.

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**Atherosclerosis of the Common Carotid and Its Significance in Understanding the Forms of the Blood Column.**

*Rudolf Beneke, Frankfurt. Ztschr. f. Path., Munich, 28:407, No. 3, 1922.*

At the point where the common carotid passes into the internal carotid artery, Chiari found a slight connective tissue endarteritis with fatty degeneration, arranged in spots with a normal media. This form is less frequent than the peculiar localization of typical atherosclerosis in a stripe running from the point of origin of the external carotid centrally toward the common carotid. The severest changes were just at the beginning of the external carotid. Sometimes sclerosis in the latter extends in rapidly decreasing degree to the thyroid artery, still more rarely to the lingual and external maxillary arteries. Centrally from its point of origin the strip, which is at first the width of the external carotid, gradually decreases but runs several centimeters directly along the axis of the vessel. Sometimes the common carotid in the affected region seems to be dilated into a shallow groove shape. In pronounced cases this stripe takes up about half of the lumen of the common carotid. The other half which runs toward the internal carotid is always quite free from sclerosis. Immediately above the point of exit of the internal carotid in the region of its bulb a not very pronounced atherosclerotic change develops, particularly a pronounced fatty degeneration of the intima. This degeneration of the intima generally shows less sclerosis than the stripe in the common carotid. But occasionally it is pronounced, especially when shallow transverse grooves complete the picture of ruptured aneurysm. The lower border of the aneurysm often ends in a sharp transverse ridge which marks the spur of bifurcation. The stripe in the common carotid generally ends by becoming gradually narrower and lower toward the heart. Often it continues further in the form of isolated striped or spotted areas of fatty degeneration. The macroscopic appearance of the chief

stripe corresponds to the ordinary picture of mild atherosclerosis. Only rarely at individual places hard smooth hyaline scleroses or calcium plaques are found, corresponding to the nodose sclerosis of the aorta at the point where the intercostal arteries are given off. The intima often shows pronounced fatty degeneration, the media seems to be quite intact. Microscopically the intima of the stripe is markedly thickened by fibrils which run chiefly in a longitudinal direction with few and delicate elastic fibers; here and there are small, flat, nodular isolated foci.

The thickened areas contain chiefly those peculiar swollen masses resembling amyloid which can easily be demonstrated in any artery by their metachromasia, and are generally attached immediately to the elastic fiber layers. The bulb of the internal carotid shows more or less pronounced thinning of the dilated media and over it fibrous new growths of the intima and extreme fatty degeneration with atheromatous necroses in all stages. At the border of the point of exit of the 2 carotid branches there is an especial strengthening of the elastic-muscular intima zone by a fiber zone which is at first predominantly circular, over which the inner layer is arranged in longitudinal fibers. The latter correspond, especially in the external carotid, to the characteristic stripes which continue toward the thyroid. Every formation of connective tissue fibers in the vessel wall, including the formation of elastic bundles, is to be regarded as the result of a traction on the corresponding parts of the wall. If we imagine a column of blood forcing its way along the trunk of the carotid until it reaches the point of bifurcation where it breaks up into the 2 branches, then any traction must take place either at the moment of the advancement of the wave or at the moment of the retrograde flow of the current owing to the resistance encountered in the vessel branches, or at both these periods. The form of the proliferated tissue stripes with their increasing thickness to the point where the external carotid is given off indicates that the local interference with outflow into this branch strengthens the retrograde flow. The retrograde wave of the pulse attains such a high energy that it exercises traction on this segment of the wall. And this same retrograde flow prevents the relaxation of the corresponding parts of the wall of the common carotid. The external carotid offers special difficulties to the advancing pulse wave. The sharp contrast between the atherosclerotic stripe in the external carotid and the normal stripe in the internal carotid shows that in the trunk of the common carotid there are always 2 streams of different lateral pressure and evidently of different propulsive force running beside each other.

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#### **Heterotopy of Bone-Marrow.**

*Helena Herzenberg, Virchow's Arch. f. path. Anat. etc., Berlin, 239:145, Sept. 27, 1922.*

Up to 1905 the appearance of bone-marrow in atypical locations was known to occur only pathologically in previously calcified places (heart, valves, arteries, kidneys, lymph-glands, muscles, cartilage). Etiologically, the condition was attributed partly to autochthonous for-

mation, partly to formation due to the introduction of myelogenous elements. Later, bone-marrow formation was recognized in atypical places without bone formation in certain systemic diseases. To the small number of such cases reported in literature, the author adds 4 of his own.

In the first case, that of a 2 year old child, the clinical diagnosis was splenic anemia (tuberculosis?). The autopsy diagnosis was: general anemia, chronic splenic tumor, tuberculosis. The spleen showed hyperplasia of the pulp, hypertrophy of the follicles and slight increase in interstitial tissue. In the liver there was an accumulation of mononuclear lymphocytes in the capillaries. In the renal pelvis, there was subepithelial extravasation of blood and myelogenous tissue in connection with numerous erythrocytes, myeloblasts, myelocytes, normoblasts, megalokariocytes, few fat cells, single mitoses.

In the second case, also of a 2 year old child, the clinical diagnosis was splenomegalic anemia and nephritis; the autopsy diagnosis, acute nephritis, fatty degeneration of the heart, parenchymatous degeneration of the liver, edema and hydrops, chronic splenic tumor, general anemia and rickets. The spleen showed brown induration, hyperplasia of the pulp and follicles. The hepatic capillaries showed many mononuclear white blood corpuscles. Under the mucous membrane of the renal pelvis were extramedullary blood-forming foci and erythrocytes, normoblasts, myeloblasts, eosinophilic myelocytes, megalokariocytes. Thus the hilus of the kidney assumes a certain importance for extramedullary blood formation in splenic anemia.

In the third case, that of a man aged 59 with vitium cordis, the autopsy diagnosis was: arteriosclerosis, aneurysm of the wall of the heart, myocardiac degeneration, atrophy of the liver and spleen. In the hilus of the liver there was a pedicled structure the size of a cherry which represented an accessory suprarenal cortex; in the latter was bone-marrow tissue. This may be said to have developed autochthonously from the epithelium of the capillaries.

In a fourth case, heterotopic bone-marrow was found in the rectus abdominis muscle of a man whose death was caused by atrophic cirrhosis of the liver. The possibility of an extramedullary blood formation must be extended to the limits of the sites known to us.

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#### **Fuchsinophilic Cells in Sputum.**

*Pietro Maria Franco, Riforma med., Naples, 38:964, Oct. 9, 1922.*

Special cells, so-called fuchsinophils, are occasionally encountered in sputum, their number averaging 16-20%, very frequently in company with the tubercle bacillus (and possessing therefore no special diagnostic value in such cases), at other times in cases giving a vague and uncertain symptomatology, with small recurrent hemoptyses, but without any clear, definite physical findings either on percussion or auscultation, in fibrous conditions, etc., where the tubercle bacillus cannot be demonstrated. They are most frequently round in shape, with sharp outline, some being slightly ovoid; they appear compact and homogeneous. They vary in size from that of a gonococcus to that of a very small red blood-cell. Their size, in addition to their staining properties, helps

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distinguish them from Mircoli-Much granules, the latter being always much smaller. These corpuscles are almost always isolated. Very rarely they may be seen intact or in process of disintegration within the large macrophages. They never exhibit the phenomenon of budding, nor do they display the special and characteristic staining properties of blastomycetes; they can therefore not be confused with the latter. They do not take the ordinary neutral fat stains (osmic acid, sudan I or III), and have in all probability nothing in common with fats. They seem to stain gray with osmic acid, and mahogany red with sudan III, after exposure to chromic acid, after the fashion of lipoid granules. They do not take the acid anilin dyes, nor the red of the Romanowsky stain, and thus cannot be confused with granular remains of red cells which, in view of some modification they seem to have undergone, resist decoloration by acids and are frequently encountered in sputum preparations. These cells are not found exclusively in milk drinkers, nor do they originate from the latter, since they are frequently met with in individuals who have taken no milk at all and fail to materialize in infants who are on an exclusive milk diet.

In addition to being acid fast, they are also alcohol fast. They are always seen quite distinctly in preparations decolorized with alcohol—Ziehl-Nielsen-Heubner, Ziehl-Nielsen, etc. They are also resistant to antiformin, although to a much lesser degree than the tubercle bacillus. In general, with respect to resistance to alcohol and to acids, these corpuscles may be considered as exhibiting physicochemical reactions, if not totally identical, at least greatly similar to those of the tubercle bacillus. Since very frequently these corpuscles precede or follow the appearance of the tubercle bacillus—which latter may not infrequently fail of demonstration in preparations subjected to antiformin treatment—their presence acquires considerable diagnostic and prognostic import.

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#### **Silicosis and Miners' Phthisis.**

*W. E. Gye and E. H. Kettle, Brit. J. Exper. Path., London, 3:241, Oct., 1922.*

There is overwhelming clinical and experimental evidence that silica induces a fibrosis of the lungs, rendering them unusually sensitive to tuberculosis. In the study of this increased sensitivity the authors made a number of experiments on mice, injecting them subcutaneously with solutions of the soluble, colloidal form of silica, or suspensions of the insoluble form. The animals were killed at stated times and the local lesions prepared for histologic examination. Within 3 hours after injection of  $\text{SiO}_2$  a recognizable microscopic lesion is produced, consisting of an area of granular coagulation necrosis, quite acellular except at the periphery where a few of the fixed connective-tissue cells of the part can be recognized, and an occasional polynuclear leukocyte. Considerably later stages of the lesion are characterized by the gradual shrinkage of the coagulum, the appearance at the periphery of large mononuclear cells with irregular outlines and vacuolated protoplasm, and the active proliferation of connective tissue with the formation of numerous capillaries. The final stages are those of an organizing inflammatory fibrosis, but the process lasts a considerable time, and the remains of the necrotic tissue persist for 10 days at least.

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This local reaction was compared with the one obtained by inoculating tubercle bacilli alone and in combination with silica. Both human and bovine strains of tubercle bacillus possess only a very slight degree of pathogenicity for the mouse. The bacillus can proliferate in the tissues, but it causes very little reaction. When present in small numbers the local reserves of the tissue appear adequate to cope with it, though when injected in massive doses it calls forth a pronounced exudation of polynuclear leukocytes. It is readily phagocytosed by the fixed connective tissue cells or polyblasts, as well as by the wandering leukocytes, although it seems likely that it can actually proliferate within phagocytes. It appears to cause no cell necrosis or tissue destruction and even when transported to secondary foci in the latter it gives rise to only a very moderate degree of tissue reaction. But the injection of tubercle bacilli accompanied by silica into the subcutaneous tissue gives rise to a much greater local reaction than an injection of tubercle bacilli alone and in addition the general dissemination is earlier and more active. Twenty-four hours after such a procedure the local tissues of the mouse showed a considerable lesion consisting of a central fine coagulum with an outer zone of leukocytes, the whole being bounded by a thin limiting coagulum. A few bacilli could be seen in the central zone. There was general congestion and leukocytosis in the neighboring areolar tissue. On the seventh day the lesion is simply a later stage of the previous ones. There is still a central mass of necrotic coagulum, though it is obscured to some extent by leukocytes, and a peripheral necrotic zone with a limiting border of granulation tissue. The number of mononuclear phagocytes has enormously increased and a considerable proportion of them contain bacilli. The appearances suggest that the bacilli which have been proliferating in the abscess are all engulfed by phagocytes, many of which wander out into the granulation tissue at the margin of the lesion.

While the authors do not claim that the processes herein described parallel those occurring in miners' phthisis, yet the presence of a definite cell poison must obviously diminish the power of the tissue reaction and so favor the progressive multiplication of the infecting bacilli. Further work along this line is proceeding.

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**The Nature of Bile Corpuscles.**

*Heinrichsdorff, Virchow's Arch. f. path. Anat. etc., Berlin, 239: 64, Sept. 27, 1922.*

The so-called bile thrombi resemble red blood-corpuscles histochemically, especially by the lipoid reaction. In a case of congenital hydrops there were red blood-cells not only in the blood capillaries, but also in the liver cells and in the bile capillaries, as well as distinct bile thrombi. Analogous conditions occur in adults, as for example in a case of acute atrophy of the liver in static icterus with focal degeneration of the parenchyma. The author believes that the bile corpuscles are derived directly from the red blood-cells, since their passage from the blood capillaries into the bile capillaries can be demonstrated, and since they correspond to the red blood-cells in their morphologic, physical and histochemical aspects. The differences concern merely color and size. This view can be explained only by assuming changes

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in the walls of the blood capillaries, and by granting that the intimate contact of the liver cells with one another has been broken and that the resistance of these cells to the penetration of foreign bodies has been decreased.

This would also be a simple explanation for the occurrence of icterus, as it seems quite plausible that there should be a passage in the opposite direction, namely that bile should penetrate the blood capillaries. A breaking down of hemoglobin may occur with the infiltration of red blood corpuscles between the liver cells. This may account for the deeper color of the bile and also for the polycholia and pleiochromia.

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**Pathologic Changes in the Muscles in Asiatic Cholera.**

*W. Warasi, Deutsch. med. Wchnschr., Leipsic, 48:1387, Oct. 13, 1922.*

The author found cloudy swelling and waxy degeneration in the striated muscle in some cases of Asiatic cholera.

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**Pathologic Anatomy of Chronic Dysentery.**

*F. von Werdt, Frankfurt. Ztschr. f. Path., Munich, 28:379, No. 3, 1922.*

Anatomy contributes more to the diagnosis of dysentery than bacteriology which, according to general opinion, completely fails, especially in chronic dysentery. By a combination of all possible changes in the same intestine the picture may be an extraordinarily complicated one. The material includes 400 autopsies in Innsbruck war hospitals, among them 52 acute cases with a duration up to 4 weeks, 59 subacute cases with a duration of 4-8 weeks and 287 chronic cases. The first changes were found in the large intestine, generally at the level of the folds which bound the haustra, and in the small intestine at Kerkring's folds; these were markedly swollen, soft, very red, generally there were small hemorrhages and in the intestinal contents there was abundant mucus. This catarrhal stage can only seldom be observed, as further changes quickly follow. Soon, at the level of the folds, epithelial necrosis develops in the form of branny, white membranes often surrounded by a hemorrhagic areola, which quickly become confluent and form in the large intestine the well known ladder-shaped figures. In a short time the necrosis extends superficially, the scabs are cast off and extensive geographic ulcers are formed; in rapidly progressive or long-continued cases extensive areas of mucous membrane may be cast off or the entire inner surface of the small intestine may be covered with the diphtheritic membrane which is characteristic of dysentery.

In many cases the process is most advanced in the rectum where it begins and it decreases in intensity and age toward the mouth. Finally the mucosa and submucosa may be entirely destroyed over long stretches and the muscularis be clearly visible, often the serosa is reddened and covered with fibrin. In some cases the intestinal follicles are involved; frequently they show medullary swelling, though to a less degree than

in typhoid, and also sharply circumscribed necroses. In addition to these catarrhal and necrotic processes there may be multiple suppurations caused by mixed infection, localized generally in the follicles. Often the process extends not only superficially, but also to the submucosa and undermines the mucosa over long stretches. In some cases, very severe changes are observed in the lower small intestine. In the subacute stage, which is hardly distinguishable clinically except by the duration of the disease, there is anatomically only a multiplication of the phenomena, the small abscesses especially increase in number, and a pronounced thickening of the muscularis begins, a hypertrophy which is caused by long-continued tenesmus.

In the acute stage the parenchymatous organs generally show only cloudy swelling, but in the subacute stage pronounced fatty degeneration is more frequent. The heart particularly is involved and may show a high degree of brown atrophy. Edema is frequent (riding-boot edema). The suprarenals show no pronounced changes but lichen pilaris cachecticorum seems to be pathognomonic to a certain extent. The chronic stage begins at about the eighth week. Its characteristic feature is hypertrophy of the musculature and the presence of healing processes beside fresh exacerbations. Among 247 cases the author saw only 40 of pronounced follicular change, but generally there were ulcerations which penetrated far into the deep tissues. In all of these cases the peritoneum was involved. Deep ulcers cleanse themselves like typhoid ulcers; their base is formed by cicatricial tissue which is shiny like a tendon. The hemorrhagic purulent intestinal contents are mixed with round, tolerably compact clumps of mucus (Virchow's tapioca bodies), which prove to be undigested starch. The anatomic changes are not at all in proportion to the severe clinical symptoms; there may be very severe cachexia with only slight intestinal changes. The most striking finding is the enormous general atrophy. Generally all the fat has disappeared or undergone serous atrophy; the author saw in very large people hearts the size of a child's fist and of a weight of 160-170 gm. Lichen pilaris cachecticorum is almost a constant finding.

Frequently there are disturbances of stomach secretion in the form of gastric achylia, and dysenteric changes of the stomach mucous membrane are also described. In bacillary dysentery liver abscesses are rare; generally they are caused by the accompanying cocci. Tuberculous changes of the lungs are frequently found, generally combined with intestinal tuberculosis. Often rheumatic pains are reported in the beginning of the disease and after a few days dysenteric stools begin. The prognosis of the disease is fatal; death occurs from exhaustion or from intercurrent disease. There is no anatomic difference between Shiga and Flexner dysentery.

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**Metabolism of Lipoids and Fats in the Liver Cells of Fasting Animals and Those Intoxicated by Phosphorus. I.**

*J. Salvioli and I. Sacchetto, Frankfurt. Ztschr. f. Path., Munich, 28:111, No. 1-2, 1922.*

In the livers of guinea-pigs in completely normal anatomic and functional conditions there are special elements of spherical form which

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have all the characteristics of liver cells but differ from these in the presence of a certain number of droplets in their protoplasm which show the microchemic reactions of lipoids. In the livers of fasting animals while the neutral fats and fatty acids which were formerly present slowly disappear, in their place in the liver cells there can be demonstrated substances that have all the characteristics of the lipoid complexes. In the dog the lipoid fatty degeneration affects all the liver cells without exception; the protoplasm of the cells around the nucleus becomes infiltrated. In guinea-pigs only a limited number of the cells change. In the livers of both dogs and guinea-pigs after long fasting, or in those that have been intoxicated with phosphorus, neutral fat is undoubtedly present in cells which did not formerly contain it and it is considerably increased where it was already present. There are always also disturbances in the circulation and in the cell structure which may often reach a high degree. There is a form of fatty degeneration of the liver caused by neutral fat; this is seen in its purest form in normal dogs that have been intoxicated with phosphorus; in fasting dogs and guinea-pigs it is connected with a certain degree of lipoid fatty degeneration. There is therefore a considerable degree of difference between the fatty degeneration of fasting and that of phosphorus intoxication.

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**Metabolism of Lipoids and Fats in the Liver Cells of Fasting Animals or Those Intoxicated with Phosphorus. II. The Finding of Intracellular Lipoids in the Phosphorized Fatty Liver.**

*Italo Sacchetto, Frankfurt. Ztschr. f. Path., Munich, 28:131, No. 1-2, 1922.*

In the phosphorized fatty liver the lipoids are increased as compared with normal. In order to exclude any injury of the digestive tract, some guinea-pigs were intoxicated by giving phosphorus subcutaneously. It was found that phosphorus intoxication, when it was brought about without any injury to digestion or absorption, did not in itself cause any increase in the intracellular lipoids of the liver. The lipoids which were found could not be regarded as in any way dependent on the direct action of the phosphorus. It remained to determine why the lipoids in the liver increased when the animals were intoxicated by giving the phosphorus by mouth: whether it was a result of some action of the phosphorus absorbed from the intestine, or of the condition of fasting, which causes inflammation of the stomach and intestine by disturbance of the absorptive capacity of the mucous membrane in the guinea-pig. Guinea-pigs were again injected subcutaneously in order to exclude the caustic necrotic action, but they were also allowed to fast from that moment on. This time there was an increase in the lipoids and lipoid-containing elements of the liver, which, though it did not reach the degree of the lipoid fatty degeneration after fasting, yet showed all its characteristic peculiarities.

The increase in liver lipoids, therefore, only occurs when the action of hunger is associated with that of subcutaneous administration of phosphorus, on account of the exclusive action of the former, or when the phosphorus is given by mouth. Phosphorus of itself does not cause an increase in intracellular lipoids. Finally guinea-pigs were injected

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with phosphorus subcutaneously and then fed normally and killed 12-24 hours after the injections. Here too there were no other lipoids found than those that appear normally, nor were they more abundant. Also in the first period of phosphorus intoxication, whether the fatty degeneration has already begun or not, the intracellular liver lipoids do not change either their normal amount or their distribution.

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**Experimental Study of Vesicular Degeneration of the Liver Cells and Water Intoxication of the Cells in General.**

*Bernhard Fischer, Frankfurt. Ztschr. f. Path., Munich, 28:201 No. 1-2, 1922.*

The characteristic and determining feature of vesicular degeneration of liver cells is not primarily the formation of vacuoles, but an enormous enlargement and distension of the whole cell, which becomes an almost empty vesicle filled only with water. At the same time the nucleus is severely injured and, in most cases, shows pyknotic contraction. In this process small and large vacuoles readily develop in the cell body. The distension of the entire protoplasm may be so uniform, however, that there is clearing up of the whole cell body with no evidence of distinct vacuoles. Since with the present methods of examination no fat, pigment or glycogen can be demonstrated in the vesicular cells, the conclusion may be drawn that the metabolism of these cells is at least greatly decreased. This is further indicated by the severe disease of the nucleus, which finally ends in its dissolution. As there is no storing of material, the vesicular degeneration of the cells can only be attributed to the absorption of water. The thin, aqueous solution does not correspond completely to water in color and consistency, because of the necroses which dominate the picture as opaque white spots. The vacuole formation in the cell protoplasm may also develop from the swelling of preëxisting granules or mitochondria; the chondriosomes, whose form is changed by every variation from isotonia, swell with falling osmotic pressure on being transferred to hypotonic salt solution and are transformed into large drops. The cell protoplasm thereby becomes loosened, the cell swells and is enlarged. Hypertonic solutions cause great loss of water and decrease in size of the cell, the protoplasm of which becomes denser and stains more deeply. The clear cells, described particularly by Adler, have nothing to do with vesicular degeneration, as they are young, growing and multiplying cells. They are distinguished from the degenerative forms by their size and the structure of the protoplasm and nucleus. True vesicular degeneration can be produced in the liver by the experimental ligation of the common duct and obstruction icterus. The stasis of the bile and water may produce a toxic action. But in ligation of the common duct there is also a disturbance in lipid metabolism which must be regarded as a third factor. The longer and more complete the occlusion of the bile duct, the more marked the esterification of the blood cholesterin and the more free cholesterin circulates in the blood. But vesicular degeneration of liver cells is particularly caused by certain toxins. Among these are phosphorus, probably also arsenic, cocain, phenylhydrazin, granugenol, amyl hydrate and paraffin oil. The

vesicular degeneration in phosphorus intoxication is obliterated at first by the severe fatty degeneration of the cells which takes place at the same time. There is a typical and severe degeneration after cocaine poisoning, and also after phenylhydrazin. The liver cells swell with contraction of the nucleus and are destroyed; there is severe water intoxication. The cell membrane must be injured in the elaboration of the toxic substances in the liver cells. All these severe toxins are lipid soluble bodies. The normal cell is protected against water intoxication by its constitution, the structure of the cell membrane, the constitution of the protoplasm and albumin substances. The cell lipoids have an influence on the water content of the cell.

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**On Lipoid Degeneration of the Kidney, and the So-Called Myelin Kidney.**

*J. W. M'Nee, J. Path. & Bacteriol., Edinburgh, 25:425, Oct., 1922.*

The name "myelin kidney" has been applied to the rare instances in which so large an amount of doubly refracting lipid has been deposited in the organ that a remarkable macroscopic and histologic appearance is produced. Three cases of this condition were autopsied by the author, who found that the doubly refracting fat, which always contains an admixture of neutral or glycerin-ester fat, is deposited chiefly in the interstitial tissue of the cortex. This fatty material, in myelin kidneys, is at first contained within cells but later lies free in the connective tissue spaces, the outline of the cells having disappeared. In all 3 examples of myelin kidney studied by the author there was found a late stage of an intracapillary glomerulonephritis, with commencing interstitial changes and degeneration of tubular epithelium. In accounting for the extraordinary lipid degeneration found in the myelin kidney M'Nee suggests: (1) that syphilis may be concerned in the production of the lesion; (2) that the damage to the tubular epithelium in cases of myelin kidney has been more severe than is usual in glomerulotubal nephritis where neutral fat is generally found in the cells.

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**The Coincidence of Tissue Malformations and Benign and Malignant Tumors.**

*F. Pietrusky, Frankfurt. Ztschr. f. Path., Munich, 28:360, No. 1-2, 1922.*

There are relations between inhibitions of development and other malformations of organs, and tumors; this is most pronounced in tuberculous sclerosis of the brain. In neurofibromatosis authentic heredity has been demonstrated and also a striking coincidence with multiple tumors, skin fibromas or angiomas, and with pigmentation, and also frequently with different congenital developmental defects of organs. In pseudohermaphrodites malignant neoplasms were found even in youth. In developmental defects of the female sexual system kidney tumors were observed. The author himself has examined 500 cases for tumors and abnormalities in the form of the organs. It was found that malig-

nant tumors especially were combined in numerous cases with malformation defects.

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**Primary Spontaneous Tumors in the Kidney and Adrenal of Mice. Studies on the Incidence and Inheritability of Spontaneous Tumors in Mice. XVII.**

*Maude Slye, Harriet F. Holmes and H. Gideon Wells, J. Cancer Res., 6: 305, Oct., 1921.*

In a series of 33,000 autopsies on mice of the Slye stock, 25 tumors, primary neoplasm arising from renal and adrenal tissue, were discovered. That these tumors are rare in mice is proved by the fact that among the same stock there were found about 5000 other tumors. Of the 25 tumors, 16 were from the kidney, classified as carcinoma, 1; adenoma, 3; hyper-nephroma, 1; sarcoma, 7; mesothelioma, 3, and sarcoma of the renal pelvis, 1. From the adrenal there were 4 tumors: 1 cortical adenoma from a misplaced interrenal adrenal rest and 3 mesothelial tumors. The remaining 5 tumors were of the mesothelial structure characteristic of urogenital anlage neoplasms. Although this series included at least 3000 cases of mammary carcinoma, often with widespread metastases in the lungs, a secondary carcinomatous growth in the kidney was never seen. The only secondary carcinoma of the kidney observed was in 4 cases in which the primary carcinoma was in the lung, thus establishing the true neoplastic nature of lung growths. But 2 cases showed metastatic sarcoma in the kidney.

Renal tumors were distributed in equal numbers among male and female mice. Coincidence of other tumors with the renal and adrenal tumors is uncommon. Except for 1 unique case, there have been no instances of malignant tumors in mice less than 4 months of age, and few under 6 months; most of the renal sarcomas occurred between the ages of 7 months and 1 year.

The epithelial renal and adrenal tumors furnished no illustration of metastasis, but in 3 cases of sarcomatous or mesotheliomatous growths involvement of adjacent lymph-nodes was noted. A review of literature on renal tumors throughout the animal kingdom discloses but 6 other cases of renal tumors in mice, all epithelial, and no other adrenal tumors.

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**The Inheritability of Spontaneous Cancer in Mice and Its Application to Cancer in Man. Studies in the Incidence and Inheritability of Spontaneous Cancer in Mice.**

*Maude Slye, J. Radiol., 3: 454, Nov., 1922.*

Because the inheritability of any disease whatever is a problem impossible of scientific solution by the use of human statistics, the author has conducted a series of experiments in the laboratory for 12 years upon mice to determine the nature and inheritability of spontaneous cancer, and finds that a fact consistently demonstrated is its inheritability, with strong evidence against the possibility of cancer being a specific germ disease. She assumes the biologic law of heredity underlying all life to be that what goes into the germ plasm must come

out in the offspring whether one wants it or not—a law of nature, immutable, deaf to entreaty. The method of heredity worked out by Mendel in 1865 with sweet peas, and later by Cuenot and others with mice, is that when a purebred house mouse, gray, is crossed with a purebred albino, the first generation will be all gray, the tendency to pigmentation being dominant. If 2 of these hybrid grays (heterozygotes) are mated their offspring will be pure-breeding grays (dominants), heterozygous grays, and albinos (recessives) in the proportion 1:2:1. The dominant grays bred together will breed true; the recessive albinos will breed true. The heterozygous grays will again yield the 3 types in the proportion of 1:2:1. The foregoing applies both to inbreeding or hybridizing with other strains similarly derived. If a purebred albino is crossed with a heterozygous gray the second generation will be equally divided between recessive albinos and heterozygous grays, and the albinos will breed true, while the heterozygous grays will give the same 3 types. If a dominant gray is crossed with a heterozygous gray the first generation will be an equal number of dominant and heterozygous grays; the dominant grays will breed true and the heterozygous grays will give the same 3 types. In other words, if a purebred albino, into whose germ plasm no pigment-making mechanism went, is mated with a gray house mouse into whose germ plasm the tendency to pigment-making mechanism did go, the first generation will be heterozygous grays, i.e. pigment-making is dominant over the lack of pigment making, therefore the mice are gray. But into their germ plasm went from one side the absence of the pigment-making mechanism (as a unit character), and from the other side went the presence of the pigment-making mechanism (as a unit character); so, since both these unit characters went into their germ plasm, both will come out somewhere in the offspring—the law of heredity. All efficient study of heredity is the study of the behavior of unit characters; only it must be certain that the characteristics have been analyzed into unit characters which segregate out and are transmitted as such.

The author applied these principles to the study of cancer, partly to learn how to get rid of a hideous disease, and partly to throw light on general biologic problems of all tissue behavior. She found that equally by the method of hybridization and by inbreeding, if 2 mice having carcinoma of the lung (primary or secondary) are mated, there can be extracted from them a strain of 100% lung tumor mice. A similar result was obtained by mating 2 mice with mammary gland carcinoma. A test was made by mating cancer mice and absolutely noncancer mice. A cancer mouse is one whose ancestry had cancer, into whose germ plasm the cancer tendency entered, and who himself has cancer. A noncancer mouse is one which came from wholly noncancer ancestry, into whose germ plasm there went the tendency to the absence of cancer and who therefore cannot transmit it to his offspring. Into the progeny of these 2 there goes (1) a tendency to cancer, and (2) a tendency to the absence of cancer; and the first hybrid generation can and infallibly does transmit some of both these tendencies. But cancer is recessive to noncancer, and so the first hybrid generation shows none of it and throughout the author's entire experience never has shown it in a single case; but the tendency to cancer segregates out, and in the second hybrid generation it appears again, in the same organs and in the same tissues as those which show the ancestral

tumors. The author illustrates her work in a series of 17 charts, showing various combinations of cancerous and noncancerous mice. Chart 1, for example, shows 3 lines derived from parents of which the female died of carcinoma of the mammary gland, carcinoma of the lung and pseudoleukemia, the male being absolutely noncancerous. In the first generation no cancer appears. From these 3 lines were extracted (*A*) the dominant, which neither in direct descent nor in any accessory fraternities ever showed one case of neoplasm; (*B*) the recessive, 100% malignant disease, and (*C*) the heterozygous line showing both cancerous and noncancerous individuals. Also where neoplasms appeared, they were of the same types and in the same locations as those of the parent female. Chart 1 shows the segregating out and transmission as such of the noncancer and cancer tendencies and the tendency to a specificity of tissue type. Chart 3 continues part of Line *A* through 15 generations without the occurrence of a neoplasm of any sort. So the author affirms that by the right selective breeding in any heterozygous line, neoplasms can be made to occur or can be held off at will. All human statistics of this nature are based upon 2 things, both of which may be in error, the memory of the patient, and the diagnoses concerning his ancestry. But if human cancer statistics when correctly taken were biologically read, they would show as certainly as mouse statistics the inheritability of cancer. They would show that the human heterozygote carries and transmits neoplastic tendencies exactly as do mouse heterozygotes although they themselves do not develop the disease.

In a summary the author says in part: Cancer and noncancer tendencies segregate out and are transmitted as such; they are therefore unit characters. A specificity of tissue type in specific organs from ancestor to offspring segregates out and is transmitted as such; it is therefore a unit character. Since these things are unit characters it is possible to manipulate them by selective breeding and thereby to implant them indelibly in any species, or to eliminate them permanently and completely from any species. Cancer and noncancer behave as though there were respectively absent or present a mechanism fitted to control proliferation and differentiation in regenerative processes, and an animal either has this mechanism or lacks it, no matter to what species he may belong. There is, therefore, a ready and certain genetic method of escape from cancer for the individual and for the race.

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**Cancer and Parasite.**

*Isidor Kross, J. Cancer Res., 6:257, Oct., 1921.*

The experiments of Nuzum were repeated in order to determine the value of the latter's claim that a Gram positive coccus is the specific bacterium of mouse carcinoma (No. 1, Crocker Institute). In this work, additional checks and controls were employed. Two factors must be considered in an experiment of this nature: (1) the tumor cell proper; and (2) the microorganism if any. In order to eliminate the first factor, radiation and freezing were resorted to, to destroy the tumor cells. Several mice with well developed carcinoma were exposed to Roentgen rays, being given a dose known to destroy the tumor

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cells completely. The rayed tumor was then excised aseptically, and inoculated into 24 mice. Part of this tumor was cultured, following most minutely the technic laid down by Nuzum; as a control unirradiated carcinoma of the same series from another mouse was inoculated into 24 mice, and part of it also cultured as before (ascitic fluid covered by paraffin). In not a single instance did a tumor develop from the radiated cells, while the inoculation of the unirradiated tumor resulted in the usual 60% of takes at the Crocker Laboratory. This experiment was repeated with another series of mice with the same results.

The cultures from the radiated tumor were incubated for 5 days, and inoculated into 60 mice. No tumor developed in any of these mice. The microorganisms were of different kinds (long and short bacilli, streptococci, staphylococci, and diplococci). The same experiments were made with tumor cells destroyed by freezing and thawing. In 2 of the 36 mice, a tumor was discovered after the twenty-eighth day, following inoculation. The author assumes that this late appearance probably was due to the fact that not all of the tumor cells were destroyed by freezing and thawing.

In no instance did the author find the characteristic organism described by Nuzum. In his opinion, the 2 undoubted tumors in Nuzum's series (2 out of 89 cases) were spontaneous new growths.

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**The Influence upon the Growth of Transplanted Flexner-Jobling Rat Carcinoma of Hydrogen-Ions and of Various Salts in Different Concentrations.**

*Kanematsu Sugiura, Helen Miller Noyes and K. George Falk, J. Cancer Res., 6:285, Oct., 1921.*

Grafts of tumors obtained by inoculating albino rats with Flexner-Jobling rat carcinoma were immersed in different solutions of salts with various hydrogen-ion concentration. Time of immersion was from  $\frac{1}{2}$  hour to 72 hours, after which they were inoculated into rats and the growth observed for 6 weeks. The same number of rats were inoculated with untreated tumor for controls. When the treated grafts were immersed in potassium phosphate buffer mixtures for 24 hours at pH 7.0, there was no effect on the growth of the tumor (the growths were as good as the controls); no growths at all were obtained at pH 5.8, and 5.1; at pH 8.2 partial inhibition and delayed growths were found, and no growths occurred at pH 8.8, varying the concentration of the buffer mixture (from 0.6 to 1.1%) at pH 7.0, and immersing for 24 hours had no effect, the growth being normal in all cases.

Sodium chlorid (0.15 M or 0.9%) at pH 7.0 had no effect in 24 hours on the growth of the transplants; 72 hours' immersion resulted in complete inhibition of the growths. Lithium chlorid at pH 7.0 in 24 hours caused partial inhibition. Calcium chlorid at pH 7.0 inhibited or retarded the growth of the transplants. Immersion for  $\frac{1}{2}$  hour had no effect on the growths; for 5 and 10 hours resulted in partial inhibition or retardation; for 24 hours and longer was followed by complete inhibition. Immersion in a Locke-Ringer solution for

72 hours did not effect the growths. Immersion in a solution containing 3 times the concentration of the sodium, calcium and potassium chlorids in the Locke-Ringer solution for 24 or 72 hours, resulted in complete inhibition of the tumor transplants.

Histologic examination of the treated grafts showed hydropic degeneration of the general structure in greater or smaller degree. The tissue immersed in Locke-Ringer solution showed proliferating capacity while complete inhibition of proliferation resulted in the tissue treated with modified Locke-Ringer solution.

Comparing the action of protease from extracts of malignant tumors and the growth of tumors as presented in this paper, it is noted that the optimum hydrogen-ion concentration for both is pH 7.0; unfavorable conditions for both are reached more rapidly on the acid than alkaline side; the various salt solutions have a similar effect on the protease action of extracts of malignant human and rat tumor, an exception being the modified Locke-Ringer solution which has no effect on the protease action, while it inhibits the growth of the tumor transplant.

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#### **The Participation of Connective Tissue in the Experimental Production of Cancer.**

*R. Bierich, Virchow's Arch. f. path. Anat. etc., Berlin, 239:1, Sept. 27, 1922.*

Under the influence of tar, as of arsenic and the Roentgen rays, 2 stages of tissue change are to be observed; these stages are continuous with one another, but are not attributable to the same condition. In the first stage, under the influence of tar and the Roentgen rays there is an increase of certain epithelial functions, which appears as a pathologic hyperdevelopment. According to the reports in literature, this effect is also obtained from the continued influence of arsenic. In this first stage, the functions of the connective tissue are changed in that its formed elements, especially those directly bordering the epithelium, undergo a marked quantitative increase. The entire process should be considered a symptom of a physicochemical tissue change, which is incited by the same factor in both epithelium and connective tissue and differs only as the structure of the 2 tissues differ. In the second stage, the cancer extends into the connective tissue and destruction of the previous process takes place. The elastic fibers gradually disappear up to the reticulum of the vessel walls; the mast-cells also vanish and only a few connective tissue cells remain. The connective tissue fibers are much twisted and broken up into plump cylinders with blunt ends. The stroma shows in the beginning, as in the early part of Stage 1, a diffuse, gray blue resorcin coloration; this finally disappears also.

During the first stage, the reaction process in the connective tissue consists in a certain physiochemical change of its entire protoplasmic system. Under the new condition, quite different from the normal, fat appears in the connective tissue and circular elastin is deposited on the changed surfaces of the "indifferent" fibers. In the second stage, this condition is changed by the cancer, and stroma and fibers take

on apparently another physicochemical structure. As a result, the connective tissue cells again disappear and the "agglutination" of the elastin is lost. Under the influence of tar and the Roentgen rays, and, to a certain degree, of arsenic, the author was able to establish changes in the epithelium and connective tissue, which should be regarded as changes in the entire system. The reactions thus obtained are apparently according to law, and as the result of the reaction we have a chemical and physical change in the structure of the epithelium and connective tissue. With the changes in "structure" of these colloidal systems, their functions have become "pathologic." The epithelium shows the new qualities in an increased growth energy (deep growth), the connective tissue, in an increased "resistance" to the invading epithelium. A balance may be preserved for some time between these 2 biologic processes, as evidenced in the early development of cancer or in the effect of tar and arsenic. Finally, however, one or the other triumphs, and thus the fate of the entire process is decided.

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**Cystic Osteoplastic Carcinoma in Comparison with Its Denser Form.**

*Franz Josef Lang and Wilfried Krainz, Frankfurt. Ztschr. f. Path., Munich, 28: 526, No. 3, 1922.*

All the processes of new-formation of bone in a case of osteoplastic carcinosis can be very well explained by the increased activity of the system which builds up normal physiologic bone. Corresponding to the increased apposition, the absorption processes are also increased, being characterized by the appearance of multinuclear and mononuclear osteoblasts, but they do not keep pace with the increased building up of bone. In a certain case, changes in the bone could be attributed to carcinosis after carcinoma of the prostate, as carcinomas of the prostate produce metastases chiefly in bone. Because of the plugging up of vessels with cancer cells, conditions of congestion developed, apparently in the bone cortex especially, which had such an effect on the adjacent lymphoid and fatty marrow that it was transformed reactively into fibrous marrow. The young seal-ring shaped fat cells which replaced the normal fatty marrow also showed this metamorphosis. The formation of fibrous marrow took place especially near the congested vessels.

The cancerous tissue penetrated the normal and fibrous masses of bone-marrow and took possession of large areas. First the cortical areas were affected. The bone responded with osteophyte-like bone trabeculas with involvement of Sharpey's fibers and new-formation of bone borders on the individual trabeculas which were thickened in this way, and finally condensation of the spongy network took place. The absorption of bone which was also absolutely increased, was decreased in comparison with the increased apposition. The cysts appeared in the cortical areas of the bone, especially just beneath and close to the periosteum or the cartilaginous linings of the joints. Probably in these cortical areas there were conditions of fluxion which offered specially favorable soil for their development.

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**A Reticular Cartilage Papillary Bronchial Adenoma.**

*E. Knoflach and E. Marchesani, Frankfurt. Ztschr. f. Path., Munich, 28:551, No. 3, 1922.*

This tumor, found by chance at autopsy, was a sharply circumscribed tumor in the right lower lobe, round, the size of a walnut, with a yellow-white, coarsely lobular cut surface and hard in consistency. The surrounding lung tissue was compressed. Microscopically the tumor showed all the constituents of the larger branches of the bronchi except smooth muscle fibers. In the tumor there were epithelial structures with cubical and pavement epithelium, arranged in tubular and adenomatous fashion; the stroma consisted of loose connective tissue, with edematous swelling in the center and with numerous vessels. The nutrition of the epithelial structures varied depending on the local vascularity. Buried in the stroma there were islands, not very well defined, of cartilage, the most central cells of which often showed vacuolar transformation. The spaces lined with epithelium often showed ciliated epithelium. A bronchial anlage was assumed to be the starting-point of the tumor. The structure is to be regarded as a hamartoma.

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**Unsaturated Alcohols Obtained from the Fat of Ovarian Dermoid Cysts.**

*Johann Muck, Hoppe-Seyler's Ztschr. f. physiol. Chem., Berlin, 122:125, Sept. 16, 1922.*

The fat of ovarian dermoid cysts resembles that of vernix caseosa. Saponification was effected by alcoholic potassium and always repeated after separation of the unsaponifiable constituents. Finally, the residue dried in vacuum, containing the unsaponifiable elements, was taken up with petroleum ether. The consistency varied from that of a mobile olive oil to a tallowy one. The substances possessed a characteristic odor. On allowing the unsaponifiable portion to stand some time at room temperature a solid layer containing cholesterol and aliphatic alcohols separated from a bright yellow to reddish brown liquid.

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**Xanthomatous Granuloma.**

*Seyler, Virchow's Arch. f. path. Anat. etc., Berlin, 239:20, Sept. 27, 1922.*

On the basis of an examination of 10 cases, the author has sought to determine whether those lesions, designated as xanthomas and generally considered true blastomas, are not frequently pure inflammatory processes. Because of their very regular histologic structure, 4 of the reported cases should be grouped as true blastomas. The remaining 6 cases showed not only the typical honey-comb xanthoma cells, but also an abundant, dense granulation tissue with giant and round cell infiltration. The regular, lobulate structure was lacking in the latter

group. While the nature of the lesions cannot be determined by these points alone, nevertheless, the presence of an indistinct demarcation in 3 cases was in favor of an inflammatory process. Fluid stasis and excess of cholesterol are necessary factors for the development of xanthoma; an increase of blood cholesterol was also present in all the cases of xanthomatous granuloma. In blastomas, the excess of cholesterol plays no part in the growth of the stroma, while in granulomas it is supposed that the first deposit takes place in tissue already inflamed (Aschoff). Xanthomatous granulomas are more frequent than is generally supposed. Moreover, it could be demonstrated that granulomas may also occur with the peculiar xanthomas, which up to that time had been looked upon only as blastomas.

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**Presence of Special Granules in Sternberg-Paltauf Granuloma.**

*Gabriele Goglia, Pediatría, Naples, 30:960, Oct. 15, 1922.*

From the examination of numerous preparations of Sternberg-Paltauf granuloma, the author concludes as follows: It is not easy to demonstrate in absolutely every case the presence of Much's granules, which would lead to the inference that the latter are not invariably associated with the lesion. In some cases where such granules have been found (2 out of 6) it was possible (in 1 instance) to reproduce the tuberculous process in a guinea-pig. But since the material had been obtained from a section made during life and was not accompanied by a complete necropsy report, it becomes impossible to state whether there exists an absolute association between the tuberculous process and malignant granuloma. There were also noticed, in 2 cases out of 6, special acid-fast granules, impossible as yet of correct interpretation as to origin and etiologic significance. But, notwithstanding the reports of other investigators, Goglia did not succeed in demonstrating the presence of such granules in the interior of the Sternberg cells.

Along with the few Much granules and the occasional acid-fast granules, there were noticed numerous other granular formations in specimens and slides of malignant granuloma; but these latter were probably due either to artefacts (stain precipitation), to special nuclear or protoplasmic fragments, or, as clearly demonstrated by various other investigators, to products of cellular disintegration (Russell bodies, Thoma bodies, etc.).

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**Neuromas of the Sympathetic.**

*R. F. von Fischer, Frankfurt. Ztschr. f. Path., Munich, 28:603, No. 3, 1922.*

In regard to mature and immature form of nerve tumors, the author reports the findings in a still-born child: On the outer side of the left lobe of the thyroid there was a round tumor the size of a hazelnut, smooth, quite hard, with gray-red to gray cut surface without any pronounced structure. There were no metastases in any of the organs, and

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the tumor was well circumscribed everywhere. Microscopic examination: From a hard capsule which was nowhere infiltrated, vascular connective tissue septums extended into the tumor. Between these there was a tissue rich in cells, which mostly had clear vesicular nuclei without visible protoplasm, and in addition to these there were cells with nuclei about half as large, also rich in chromatin with a small border of protoplasm. These were similar in size and appearance to lymphocytes. At one place in the capsule, however, there were numerous large, roundish, pear-shaped or irregularly shaped cells, always pointed conically on one side, evidently running into a nerve process; their protoplasm was finely granular and stained well without demonstrable pigment. The nucleus was pale, clear, circular or oval with 1 or 2 pronounced nuclear bodies. The tumor was quite like that described by Marchand. In view of the only partial differentiation, it is to be assumed that the tumor was in a position to strengthen its quantitative, at the expense of its qualitative, development. The aforesaid round cells are interpreted as sympathicoblasts and sympathicogonia.

The author suggests the following new classification for neuromas of the sympathetic: (I) Ganglioneuroblastomas: (1) Maturing forms, (a) ganglioneuroma simplex; (b) ganglioneuroma immaturum; and (c) ganglioneuroma imperfectum. (2) Partially maturing forms, (a) neuroblastoma gangliocellulare; and (b) proliferating ganglioneuroma. (II) Neuroblastoma Simplex: Nonmaturing forms, (a) sympathicoblastoma; and (b) sympathicogonia. This new classification includes the most important forms described in the literature.

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### **The Experimental Production of Tar-Sarcoma in Mice and Rats.**

*B. R. G. Russell, J. Path. & Bacteriol., Edinburgh, 25:409, Oct., 1922.*

In the author's experiments 50 male mice were given weekly subcutaneous inoculations in the right flank of 10-15 mg. tar. After 8½ months 1 of the 7 surviving mice showed a small ulcerating surface at the site of the inoculation and 2 weeks later a small nodule about 1 cm. in diameter could be palpated. Microscopic examination of the growth revealed it to be a spindle-celled sarcoma showing a few mitoses. When transplanted the tumor grew slowly and in low percentage in normal mice.

Similar experiments were carried out on 40 rats and 13 months later 1 of 4 surviving rats manifested at the site of the inoculations a firm, tender and palpable nodule about 1 cm. in diameter. The nodule grew rapidly and was excised in 2 weeks. An autoplast was implanted in the other flank and was removed 3 weeks later, at which time it weighed 12 gm. The original tumor recurred, however, and there were also metastatic nodules in the left lung. Histologically the primary tumor was a polymorphic-cell sarcoma. Bipolar and multipolar mitotic figures were numerous, as were mononuclear and multinuclear giant cells with irregularly shaped nuclei. The pulmonary metastases reproduced exactly the histology of the primary growth. The author

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says the macroscopic and the microscopic appearance of these sarcomas suggests that the neoplastic change is of a very sudden character.

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**Parathyroid Tumors in Multiple Giant Cell Sarcomas (Brown Tumors) of the Osseous System.**

*Bruno Günther, Frankfurt. Ztschr. f. Path., Munich, 28:295, No. 1-2, 1922.*

In almost all cases of multiple brown tumors of the bones, changes in the parathyroids, have been tumor-like enlargements. Most of the proliferated cells of the parathyroids are cells that stain dark with hematoxylin-eosin. The function of these cells seems to be connected with rachitic-malacic disease. The size of the proliferation of the parathyroids in multiple giant cell sarcoma suggests that the osseous system is strongly affected here, either as suggested by Erdheim by a hypothetic noxa or indirectly by the abnormal function of the parathyroids. This in connection with the other pathologico-anatomic studies and the clinical course of these tumors indicates that multiple giant cell sarcomas are chronic inflammatory, or rather regenerative or deficiency, proliferations, or at any rate not true autonomic blastomas. Slight degrees of disturbance of normal parathyroid function lead by way of inflammation to rachitic-malacic clinical pictures, especially that of *ostitis fibrosa*. In excessive change of the accessory thyroids, brown tumors are associated with it as evidences of extreme productive inflammation.

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